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THE BLOOD



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THE BLOOD

A GUIDE TO ITS EXAMINATION AND TO THE DIAGNOSIS AND TREATMENT OF ITS DISEASES

BY

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WITH TWENTY-EIGHT TEXT ILLUSTRATIONS AND SIXTEEN COLOURED PLATES

SECOND EDITION

EDINBURGH AND LONDON

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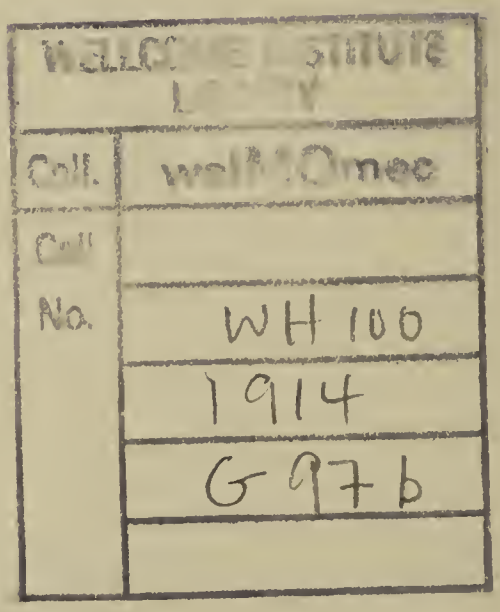
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PREFACE TO THE FIRST EDITION

Our aim in writing this book has been to put in the hands of the student and practitioner a volume giving a concise and clear account of the diseases and diseased conditions of the blood and blood-forming organs, based on a large experience of them in clinical work and in the laboratory.

We have for many years conducted post-graduate courses on the subject, and have learned how essential to a proper understanding of the blood and its diseases are a knowledge of pathology, and a clear idea of the relationship of the different elements of the blood to one another, and of their genesis. We have tried to keep our descriptions of these matters as simple as possible, and to avoid the excesses of differentiation and nomenclature in which some writers have indulged. Our explanations may not be finally correct, but we have at least found them serviceable to ourselves and others as working hypotheses, and our aim throughout has been rather to stimulate interest in a fascinating branch of study than to make a final, erudite, and conclusive exposition of the subject. For this reason we have, in the section on methods, described fully those which we have found essential or useful, and in the case of those which we have felt to be less important have referred readers to the original sources of information. In the same way we have, so far as it is possible in a work of this kind, relied in our descriptions on our own clinical and pathological experience rather than on a collation of the views of others, and we have given only those references which seemed to us essential. It would indeed be impossible to give a full list of papers on such subjects as pernicious anæmia or the leukæmias, nor is it necessary to do so, as since 1904 the world's hæmatological literature has been collected and summarised in the *Folia Hæmatologica*.

In dealing with the alterations in the blood in general diseases as an aid to diagnosis, we have felt justified in stating our conclusions

categorically, as we have for many years neglected no opportunity of testing the views of others and amplifying our own knowledge.

We have made no attempt to deal with serology, as that subject passed long ago out of the hands of the clinician, and is only now beginning to return to him in the shape of reactions, the value of which is in many cases as yet unproved.

We trust that the sections on treatment will be found useful; in them also we have relied mainly on our own experience.

G. L. G.
A. G.

EDINBURGH,
May 1912.

PREFACE TO THE SECOND EDITION

In preparing this edition the whole book has been revised and in several parts rewritten. Additions to the extent of about fifty pages have been made, and twelve new illustrations have been introduced.

Among the new matter will be found an account of new counting apparatus, dark-ground illumination, the oxydase reaction, anaplasmata, and v. Schilling-Torgau's views on erythrocyte structure. The latter are as yet unconfirmed, but they seem to us to indicate lines of research which may yield results of practical importance.

In view of the attention now being paid to the primitive forms of white cells in leukæmia, we have augmented the description of these cells, but we are not convinced of the clinical importance of many of the histological refinements. Our views on this subject are stated on pp. 193 and 194.

After the chapter on Pernicious Anæmia was in type the question of splenectomy in that disease began to assume some importance. It has therefore been discussed in an Appendix.

G. L. G.
A. G.

October 1914.

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THE BLOOD:

A GUIDE TO ITS EXAMINATION AND TO THE DIAGNOSIS AND TREATMENT OF ITS DISEASES

PART I

METHODS OF EXAMINING THE BLOOD

CHAPTER I

EXAMINATION OF FRESH SPECIMENS: ENUMERATION OF RED CORPUSCLES

Withdrawal of Samples of Blood.—For ordinary examinations blood is most conveniently obtained from the lobule of the ear and from its edge rather than its flat surface. The skin is less sensitive, and the epidermis is thinner than that of the finger. A rub with a cloth is all that is required in the way of cleaning the skin, and the slight hyperæmia thus produced causes a freer flow of blood. Antiseptic precautions are unnecessary, and cleaning with ether should be avoided, as it tends to cause a local leucocytosis. If the skin be very dirty water or soap and water may be used. Care should be taken that blood be not drawn from a dropsical part, as in that case it is diluted by water from the tissues, nor from a cyanosed part, as it is then always concentrated. For this reason also the part should always be warm. The puncture should be made with an instrument which has cutting edges. Special instruments are supplied for the purpose, but a surgical needle or a fine trocar serves admirably; best of all is a von Graefe's cataract knife, sharpened to a point rather than an edge. Sterilisation of the knife is unnecessary, provided that it is clean and bright and used for no other purpose. It may be dipped in absolute alcohol occasionally. A sharp, tapping action should be employed, and not a slow, boring movement, which is much more painful. Slight pressure may be employed to start the flow of blood, and the first few drops, which carry with them skin contamination, should be wiped off.

Only blood which escapes without pressure and fairly freely should be used.

Caution.—In cases of hæmophilia and in some cases of leukæmia and pernicious anæmia bleeding from a puncture may not readily stop. In such cases it is preferable to take blood from the finger, where, if necessary, a bandage can be readily applied.

The beginner may readily obtain samples of his own blood for examination (when accuracy is not an important consideration) by winding a handkerchief round the proximal phalanx of the thumb and then flexing the



Fig. 1.—Fibrin Network in Normal Conditions.

phalangeal joint. The congested skin over the back of the terminal phalanx after a slight puncture yields a copious supply of blood which stops on extending the thumb and starts again on flexion, and thus successive drops may be obtained without a corresponding number of punctures.

Examination of Fresh Blood.—As blood exudes after a puncture its colour and fluidity should be noted. For microscopic examination a drop of blood is touched with a cover-slip, which is then placed on a slide. Practically all the information that this method yields is better given by stained films.

Rouleaux formation[1] may be noted. It is deficient when there is deformity or alteration in size of the red corpuscles.

The *shape* and *size* of the cells are seen in this way with the minimum of artificial distortion.

[1] See Wiltshire, *Journ. of Path. and Bact.*, xvii. 1913.

The *proportions* of *cells* and their *characters* are better made out in stained specimens.

The Fibrin Network.—The density of the fibrin network can be studied in fresh specimens which have stood for fifteen minutes. Only a small amount of light should be used. The fibrin threads will be seen forming a network, and in many cases radiating from a little clump of blood-plates.

The fibrin network is increased in pneumonia, acute rheumatism



Fig. 2.—Fibrin Network Increased.

and inflammatory conditions. It is unaltered in malignant disease and markedly diminished in pernicious anæmia.

It is important in clinical work that samples of blood should be obtained with the least inconvenience to the patient. One puncture should be sufficient for an ordinary routine examination. The procedure will be stated after discussion of the different methods in detail.

Enumeration of the Red Corpuscles.—The number of red cells in a unit of blood is too great to count, and therefore the sample must be diluted. The diluting fluid must fulfil two conditions—it must prevent coagulation, and it must not affect the red cells by osmosis, *i.e.* it must be isotonic. Many formulæ have been suggested.

1. As useful as any is ordinary physiological salt solution, sodium chloride, 0·9 per cent. It has the advantage that almost any of the dye stuffs may be dissolved in it.

2. Gowers' solution—

Sodium sulphate	104 grs.
Acetic acid	1 drm.
Distilled water	6 ozs.

3. Hayem's solution—

Perchloride of mercury . . .	0·5 grm.
Sodium sulphate	5 grms.
Sodium chloride	1 grm.
Distilled water	200 c.c.

This solution is deservedly the one most commonly used. It preserves well both the shape and colour of the red corpuscles. It keeps well, though a deposit forms after a time. This can be filtered off without spoiling the solution.

4. Toisson's solution—

Sodium sulphate	8 grms.
Sodium chloride	1 grm.
Methyl violet 5 B	0·025 grm.
Glycerine (neut.)	30 c.c.
Distilled water	160 c.c.

This solution stains the nuclei of the leucocytes while conserving the red cells. Some of the latter, however, when pale, are not well seen, and the count is therefore apt to be too low. The methyl violet sometimes precipitates, and there is no great practical advantage in the staining of the leucocyte nuclei.

The Thoma-Zeiss Hæmocytometer.—This instrument, or one of its modifications, is in common use, and is very convenient. It is designed to indicate the number of corpuscles in a cubic millimetre of blood. As supplied it consists of two pipettes and a counting chamber. One pipette has a fine bore and a large bulb by which a sample of blood may be diluted either 100 or 200 times, the other has a wide bore and a small bulb by means of which blood may be diluted either ten or twenty times. The latter is specially intended for the enumeration of white cells.

In the case of the red cell pipette, if blood be taken up to the mark 0·5, and diluting fluid up to the mark 101, the dilution will be 1 in 200; if blood be taken up to the mark 1, and diluting fluid to the mark 101, the dilution will be 1 in 100. The most convenient dilution is 1 in 200, unless the blood be very poor in corpuscles, when 1 in 100 should be used.

The counting chamber consists of a round glass table surrounded by a trench, and then by a square glass plate 0·1 mm. higher than the counting chamber (Fig. 4). The central area of the counting table is divided by microscopic ruling into sixteen sets of sixteen squares. Each square is $\frac{1}{400}$ mm. in area. The squares round each set of sixteen

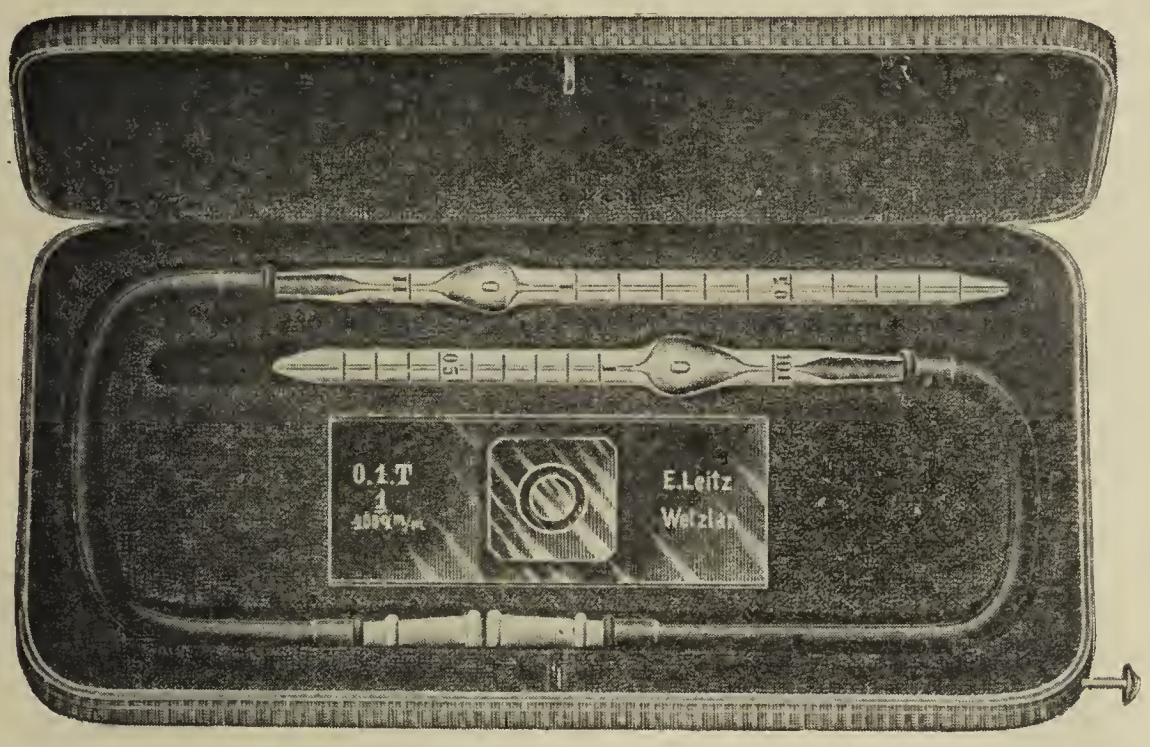


FIG. 3.—THE THOMA HÆMOCYTOMETER.

are bisected for the sake of clearness (Fig. 6). A cover-slip ground flat is supplied with the instrument, and when this is applied the depth of the counting chamber is $\frac{1}{10}$ mm.

Procedure.—The diluting fluid to be used should be at hand in a bottle, or a little may be poured out into a watch-glass. The ear is punctured, and the first two drops of blood are wiped off. As soon



FIG. 4.—SECTION OF COUNTING CHAMBER.
(The cover-slip is raised for clearness.)

as the next drop of blood becomes as big as a split pea some of it is sucked into the pipette as far as the mark 0·5. A little practice is requisite in order that this may be done accurately and smartly, and in certain conditions where coagulation time is short rapidity of manipulation is necessary. The point of the pipette is more easily held steady if the little finger rests on the patient's cheek. The rubber tube attached to the pipette should be long enough to allow the operator to look at right angles to the top of the advancing column of blood so as to note exactly the point it has reached. If too much blood

be taken up it is not easy to blow out just the amount of the excess, but frequently a small excess may be got rid of by merely stroking the point of the pipette with the finger. If the excess be considerable the blood should be drawn up to the mark 1. As soon as the blood stands at the proper mark any blood adhering to the outside of the pipette should be wiped off and the point of the pipette plunged into the diluting fluid, which is sucked up, while the pipette is gently rolled to ensure thorough mixing, until the mixture reaches the point 101. If the mixture slightly passes this point it does not greatly matter. It is of much greater importance that the 0·5 mark should be reached exactly. The pipette is now held by placing the finger and thumb at the ends and shaken vigorously, or it may be held in the horizontal position and rolled between the finger and thumb for half a minute, so that the blood is thoroughly mixed with the diluting fluid. The mixing is facilitated by means of a glass bead contained in the bulb. As the



Fig. 5.—To Show Method of Applying Cover-glass.

long limb of the pipette contains diluting fluid only, nearly half of the contents of the bulb should be blown out in order that a sample from the bulb may be obtained. A drop of the diluted blood is now blown out or allowed to drop out upon the centre of the counting chamber. This drop should be large enough to cover at least three-quarters of the central area without overflowing into the surrounding trench when the cover-glass is applied. In this matter again practice is requisite. The cover-glass supplied is ground flat, and care should be taken that its thickness does not exceed the focal distance of the objective to be employed.

A $\frac{1}{6}$-inch lens is very suitable. The counting chamber and cover-glass should be absolutely clean and should fit accurately, so that when applied to each other Newton's colour rings should be visible. They are more easily obtained with some instruments than others.

The application of the cover-glass always presents difficulties to beginners. It must be done quickly, for the corpuscles at once begin to settle on the ruled area, and as the drop of diluted blood is convex, this rain of corpuscles is greatest at the centre, so that delay causes uneven distribution. The cover-glass should be lowered obliquely, one

side being allowed to rest on the outer square and held steady with the fingers of the left hand, the other lowered gradually on to the drop, at first with a needle, but as practice makes it easier, with the fingers of the right hand. Another method which may be of service to the beginner is to fix the cover-slip against the edge of the outer square with the left forefinger and then push it down with the right, using the edge of the square as a fulcrum (Fig. 5). The counting slide should then be held level with the eye and between it and a light source to

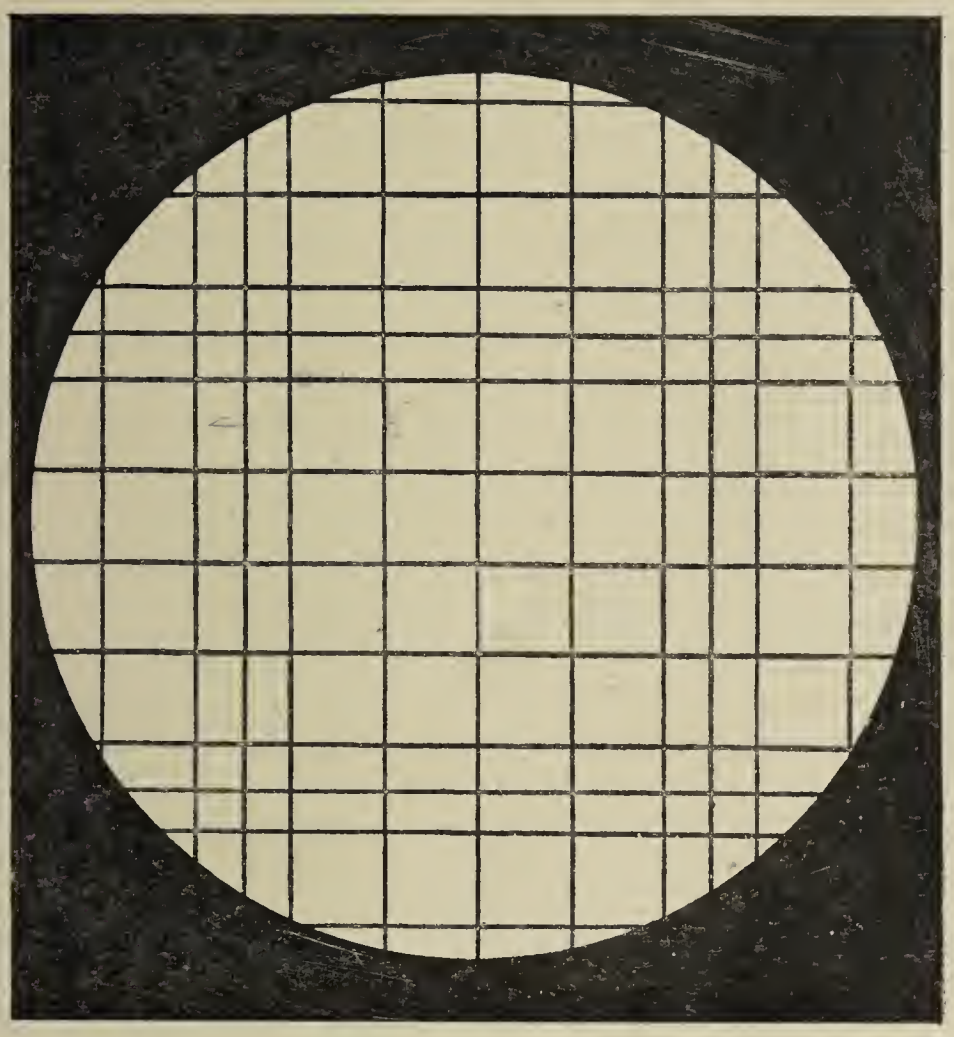


Fig. 6.—Part of the Counting Field under the Microscope.

make sure that Newton's rings have appeared. It should next be examined with the low power of the microscope. If air-bubbles be present the preparation is useless, and the slide and cover-glass must be cleaned and a fresh preparation made. The same must be done if the corpuscles are not evenly distributed, right to the edge of the drop. The most usual error is that they are too thickly crowded over the centre of the ruled space. It is impossible to lay too much stress on even distribution, for upon it the accuracy of the count hinges entirely. The figures quoted in the annexed example give about the maximum range of allowable divergence. If the range is greater a fresh preparation should be made after the fluid in the bulb has been again

thoroughly shaken up, and that which has been lying in the long limb of the pipette expelled.

Türk[1] has suggested that a very small drop of the diluting fluid should be placed under two opposite corners of the cover-glass. Although this procedure might be objected to on theoretical grounds, there is no doubt that the capillary attraction of the fluid gives good contact, and the colour rings are more readily brought out.

The number of corpuscles in a large number of squares must now be counted in order to find the average number per square. In counting the corpuscles in a set of sixteen squares all those on interior lines must be included, but only half of those on the lines bounding the half squares must be counted. This may be carried out by counting all the boundary line cells on the left and top, and omitting all those on the right and foot. It is convenient to count the number of cells in five sets of sixteen squares, *i.e.* in a total number of eighty squares and divide that number by 80 to find the average per square. To find the number per cubic millimetre we must multiply this average number by 400 (the area of each square being $\frac{1}{400}$ mm.) and by 10 (the depth of each square being $\frac{1}{10}$ mm.) and by 200 (the extent of the dilution). Suppose the numbers counted were as follows:—

In the first set of	16	squares	. . .	108
,, second	,,	,,	. . .	96
,, third	,,	,,	. . .	98
,, fourth	,,	,,	. . .	120
,, fifth	,,	,,	. .	121
In	80	squares	. . .	543

$$\frac{543 \times 400 \times 10 \times 200}{80} = 5{,}430{,}000 \text{ per c.mm.}$$

It may be noted that when the number of corpuscles in eighty small squares is counted, the addition of four cyphers at once gives the number per cubic millimetre, when the dilution is 1 in 200.

In making the enumeration a rather small diaphragm should be used, and if a substage condenser is employed, it should be a little lower than the position for examining stained specimens.

It is convenient to arrange the combination of objective, tube-length, and number of eye-piece so that the visible field just exceeds the sixteen small squares which are being counted.

[1] *Vorlesungen über klinische Hämatologie*, 1904.

It is only in hospital and consulting-room that the corpuscles can conveniently be counted immediately the pipette is filled. When this is done at a distance from a microscope a rubber band of appropriate length and fair thickness is slipped over the ends of the pipette. This seals the openings, and the pipette can then be replaced in the box and

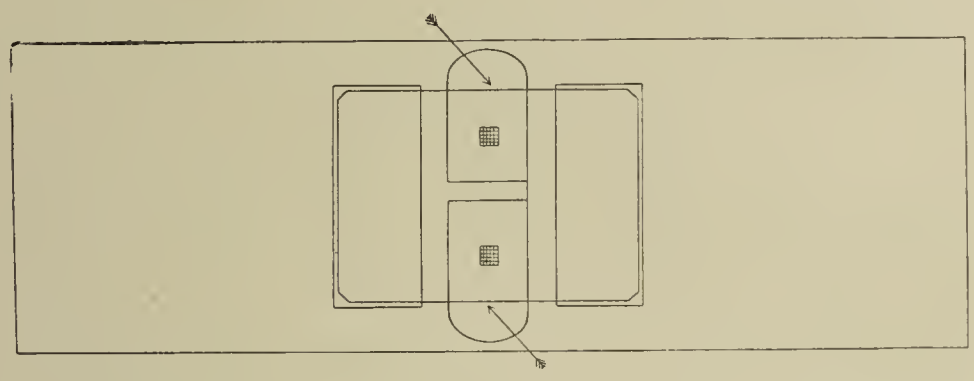


FIG. 7.—BÜRKER'S COUNTING CHAMBER WITH COVER-SLIP APPLIED.

(The arrows indicate where the drop of diluted blood is to be placed.)

taken home. Care should be taken that the pipettes are kept approximately level in transit—the box should be carried at the bottom of a bag rather than in the coat-tail pocket—lest a proportion of the corpuscles escape into one or other limb of the pipette. Presumably the pipettes might be left indefinitely and the counting done at any

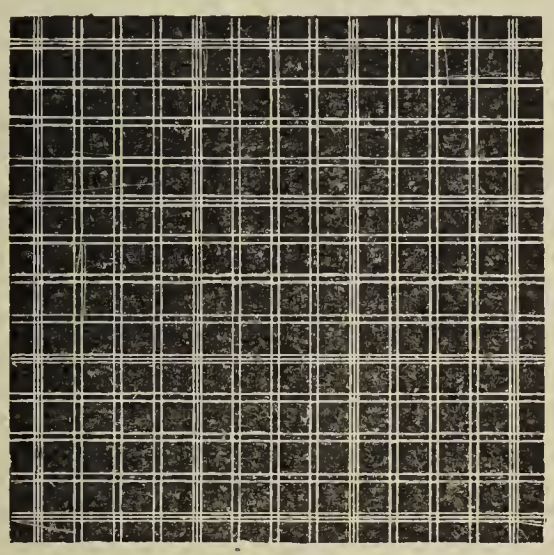


FIG. 8.—RULING ON BÜRKER'S COUNTING CHAMBER.

future time, but the corpuscles are apt to stick together. We have obtained an even distribution at the end of three days, but do not recommend so long a delay. The longer the pipette has been allowed to lie the more thorough must be the shaking and rolling before the count is carried out.

After use the instruments must be very thoroughly cleaned (see Chap. III.).

Bürker's Hæmocytometer.[1]—This is an important modification of the Thoma-Zeiss instrument.

The counting chamber is bisected by a transverse channel. On each side of the counting plate there is a rectangular piece of glass arranged to leave a gap between its inside edge and the side of the counting table. The side plates are 0·1 mm. higher than the counting plate. The counting plate has on each side of the central division the ruling shown in Fig. 8 over an area of 3×3 mm. Each small square corresponds to one square of the Thoma-Zeiss ruling, and each large square corresponds to sixteen squares.

In another form of the instrument there is a simple stage micrometer and a number of square stops of different size to fit into the eye-piece. The size of the eye-piece aperture is determined by means of

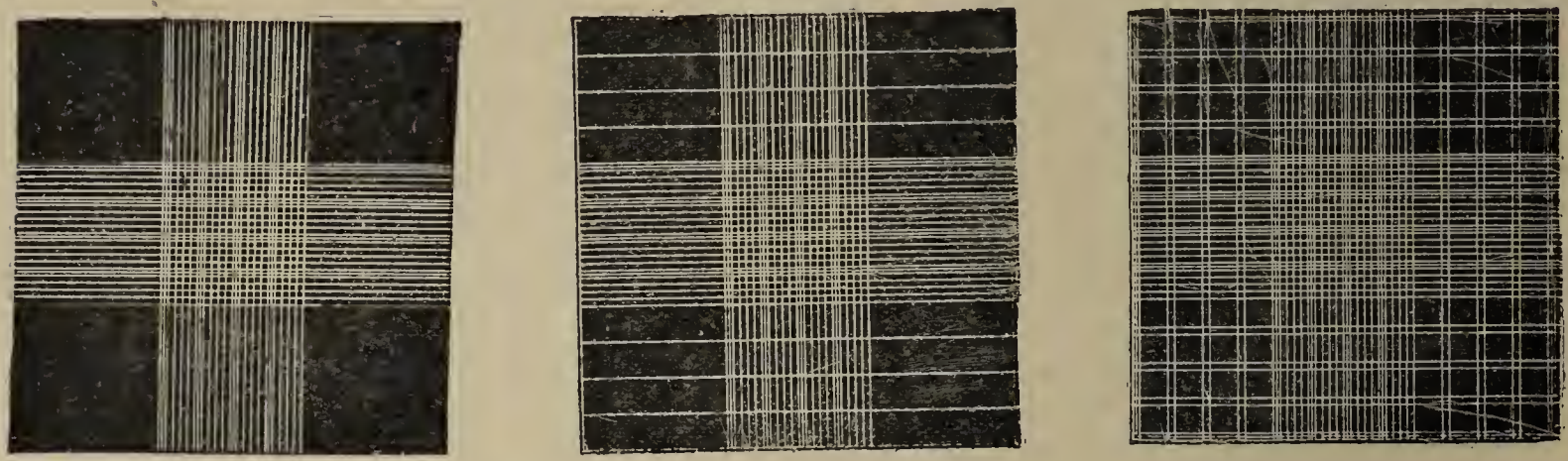


Fig. 9.—The Thoma, Zappert, and Türk Hæmocytometer Ruling.

the stage micrometer (the magnification being adjusted by the use of the draw-tube) and then the corpuscles are counted in a series of microscopic fields of known extent and of course 0·1 mm. depth.

We prefer the first type of instrument, and instead of Bürker's ruling we use that of Türk (Fig. 9).

To use this counter the cover-slip is first applied. A drop of diluted blood is then placed on the counting table at the edge of the cover-slip, and just the right quantity finds its way into one side of the counting plate by capillary action.

The advantages claimed for this instrument are—1. That all difficulty in the way of filling the counting chamber with the right amount of diluted blood and of applying the cover-glass is eliminated.

2. That there is no time for deposition of corpuscles before the drop of diluted blood has spread out, and that distribution is therefore more even.

3. The double counting chamber permits of a check enumeration without disturbing the cover-glass.

[1] *Pflüger's Archiv*, cvii. 1905, 426.

Counting Chambers of Zappert and Türk.—Many modifications of the Thoma-Zeiss ruling have been introduced with the idea of affording a larger counting area than is provided by the Thoma-Zeiss instrument. This is specially desirable when leucocytes are being counted.

The following may be taken as types of a very large number[1]:—

Zappert's Counting Chamber.—The central area corresponds to that of the Thoma instrument, but the peripheral area is ruled into larger squares. The whole area of 3×3 mm. is divided by heavy cross ruling into nine large squares, each equal in area to the central area of 400 small squares. The whole ruled area therefore corresponds to 3600 small squares. The peripheral squares are for convenience divided into four, each quarter corresponding to 100 small squares.

Türk's Counting Chamber.—This is similar to the Zappert instrument, but the large peripheral squares are divided into areas corresponding to sixteen small squares and each of these areas is in turn surrounded by lines corresponding to those which enclose the bisected squares of the central area.

Gowers' Hæmocytometer.—This instrument consists of a pipette graduated to measure 5 c.mm. of blood, a second pipette to measure 995 c.mm. of diluting fluid, a mixing chamber with stirrer, and a counting chamber. The instrument is not so convenient as the Thoma hæmocytometer. The squares on the counting chamber are $\frac{1}{10}$ mm. in area, and the depth when the cover-slip is applied is $\frac{1}{5}$ mm. The number of corpuscles in ten squares multiplied by 10,000 gives the number in a cubic millimetre of undiluted blood.

Hæmocytometers of Hayem and Malassez.—These instruments are now almost entirely replaced by the foregoing.

Durham's Pipette.[2]—One of the short thick-walled capillary tubes introduced by Oliver, having a capacity of 5 or 10 c.mm., is fixed by means of a cork in one end of a glass pipette. The other end of the pipette is fitted with a rubber cap, which has a side perforation. A separate measure for diluting fluid is required, and a small test-tube containing a glass bead is used as a mixing chamber. When brought into contact with a drop of blood the capillary tube fills itself. By compressing the rubber nipple in such a way that the perforation is closed the blood is expelled into the measured diluting fluid. The process may be repeated with the diluted blood to ensure complete washing out of the blood from the capillary tube.

[1] Illustrated examples will be found in Leitz's catalogue.

[2] *Edin. Med. Journ.*, 1897.

Hirschfeld's Pipette.[1]—This instrument ensures great accuracy of measurement, but is difficult to clean, and entails the use of a separate mixing chamber. Diluting fluid is first sucked up into the bulb. The stop-cock is then reversed and the excess is blown out. Blood is now sucked up, and by again reversing the stop-cock blood and diluent can be blown out into a mixing chamber.

Pappenheim's Pipette.[2]—In this instrument the rubber tube of the Thoma-Zeiss pipette is replaced by a closely-fitting glass cap. By a syringe action suction can be exerted on the blood and diluting fluid.

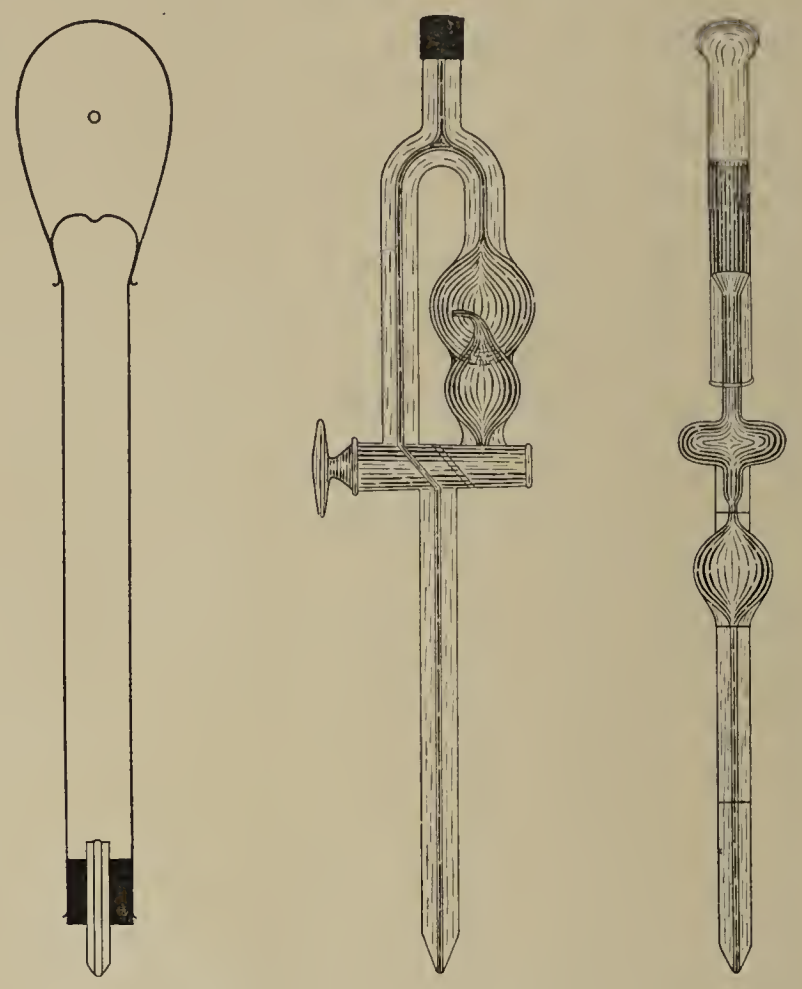


Fig. 10.—Pipettes of Durham, Hirschfeld, and Pappenheim.

Oliver's Tintometer.—This instrument does away with the necessity for microscopic work, and affords a rapid means of estimating the number of red corpuscles. It consists of a rectangular test-tube, whose mouth measures 15 mm. by 5 mm., a self-filling capillary tube of 10 c.mm. capacity, and a rubber-capped pipette with about a quarter inch of rubber tubing at its end. The test-tube is calibrated by placing in it 10 c.mm. of normal blood and diluting it with Hayem's solution. Daylight must be excluded, and a candle at a distance of about 4 ft. is looked at through the narrow sides of the tube. The dilution is continued until a bright horizontal line is seen on the glass. This line is made up of numerous minute images of the candle produced by the

[1] *Folia Hæmatologica*, xii. ; *Centralb.*, 1911, 245.
[2] *Deutsche med. Wochenschr.*, 1912, 2067.

longitudinal striation of the glass. This line is marked 100, and corresponds to a blood-count of 5,000,000 per c.mm.

To use the instrument a small quantity of Hayem's solution is first dropped into the test-tube. The capillary tube is now filled by holding its point horizontally in a drop of blood. Its point is wiped. By means of the capped pipette, which is fitted to the more pointed end of the capillary tube by the rubber tubing, the blood is expelled into the test-tube.

Hayem's solution is now added until the bright horizontal line

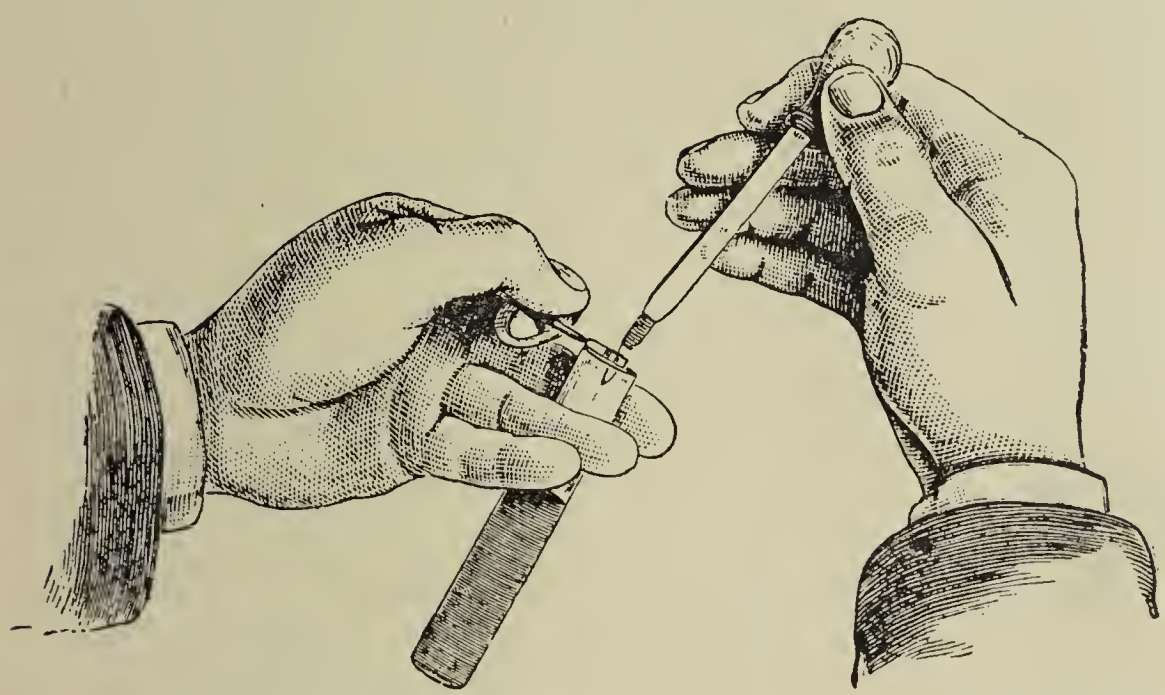


Fig. 11.—Method of Using Oliver's Tintometer.

appears, and the percentage of red cells is read off at the level of this line. This instrument is accurate for blood not too markedly abnormal. It requires a dark room, and is perhaps more suited for the laboratory than for clinical work.

The Hæmatocrit.—This instrument has not found a great deal of favour. It consists of a graduated capillary tube, which is filled with blood and then centrifuged. The height of the column of the corpuscles gives an indication of their number. Alterations in shape or elasticity of the corpuscles are factors which may influence the results of this procedure. In health the proportion of plasma to volume of corpuscles is roughly two to one. Capps[1] uses the term "volume index" to express the relationship between the volume of the corpuscles and their number. The volume expressed as a percentage of the volume in health is divided by the number of red cells as counted by the Thoma hæmocytometer, and expressed as a percentage of 5,000,000.

The index is high in pernicious anæmia, practically normal in cases of moderate secondary anæmia, and low in severe secondary anæmia.

[1] *Journ. of Med. Research*, 1903.

CHAPTER II

ENUMERATION OF LEUCOCYTES AND BLOOD-PLATES

Enumeration of Leucocytes.—The Thoma hæmocytometer or a modification is commonly used. The pipette with a wide bore and small bulb is employed. Blood is sucked up to the mark 0·5 and diluting fluid up

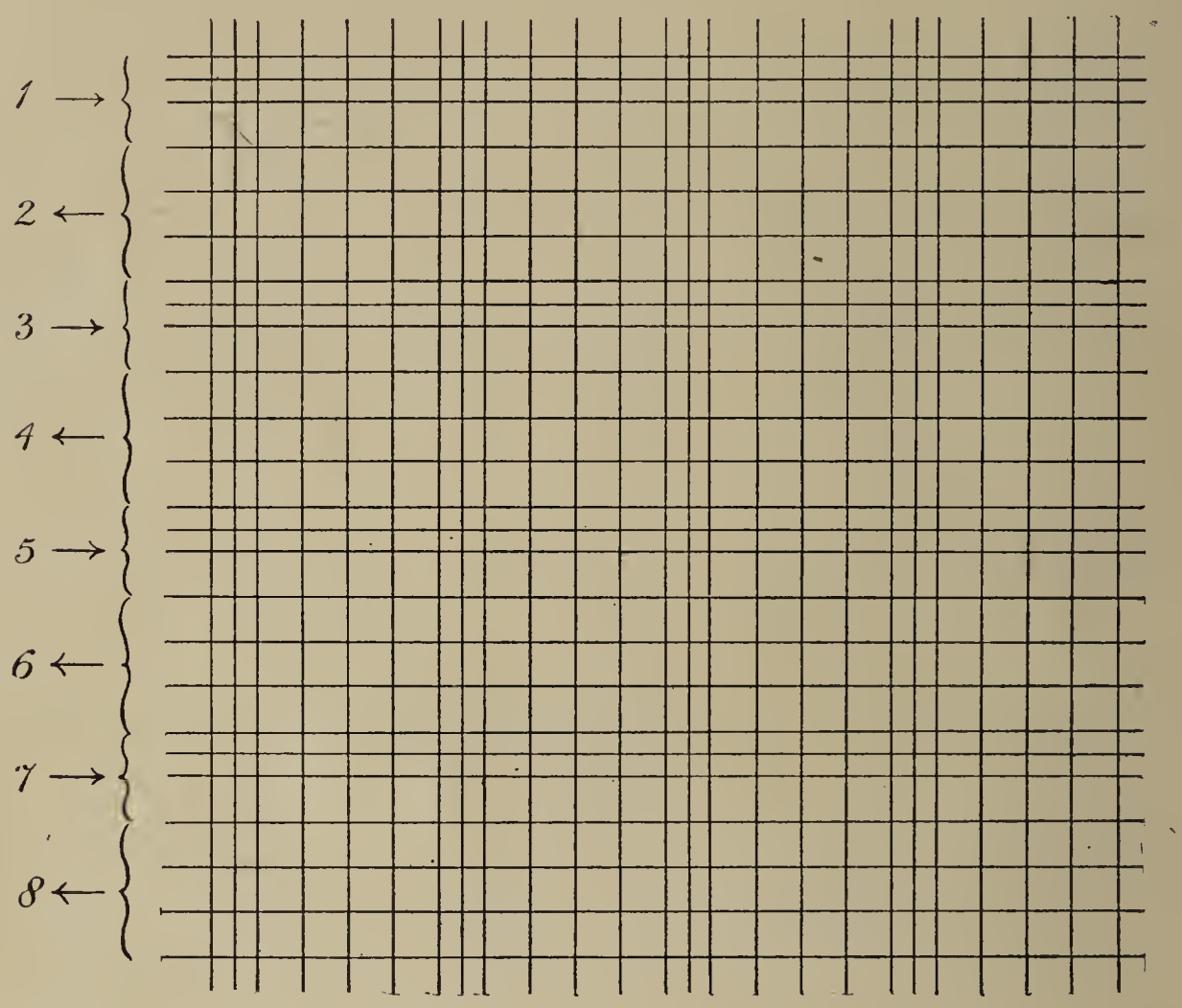


Fig. 12.—Method of Counting Leucocytes.

to the mark 11, giving a dilution of 1 in 20. If blood be sucked up to the mark 1 the dilution will be 1 in 10. Owing to the wide bore of the pipette it must be kept horizontal to prevent fluid escaping. The diluting fluid should "lake" the red corpuscles and show up the white cells. One which fulfils these requirements is 1 c.c. of glacial acetic acid in 100 c.c. of distilled water to which enough methyl green has been added to colour the solution a fairly deep green. The acetic acid renders the nuclei sharp, the methyl green tints them faintly. The

procedure is exactly the same as in counting the red cells and the same counting chamber is used. As their numbers are small, the leucocytes in a large number of squares must be counted in order to obtain an average. It is advisable to count the white cells not only in the whole sixteen sets of sixteen squares but also in the divided squares surrounding the sets. The total number of squares is then 400. In making the enumeration a mechanical stage is a great advantage.

We make the count by beginning with the square at the top left-hand corner as it appears under the microscope and place the slide so that a row of bisected squares is at the top. Moving the field from left to right we count all the leucocytes in the two top rows of squares, *i.e.* the top row of half squares and the row of whole squares below it. Moving the field up we then count from right to left all the leucocytes in the next three rows. The number may be jotted down and then the process is repeated three times. Suppose the dilution has been 1 in 10 and the actual number counted was 70. That number divided by 400 gives us the average number per square.

$$\frac{70 \times 400 \times 10 \times 10}{400} = 7000 \text{ per c.mm.}$$

Note that (when the dilution is 1 in 10) the number counted multiplied by 100 at once gives the number per cubic millimetre.

It is, of course, quite possible to count both red and white cells at the same time by using the same pipette. This plan is useful in counting the leucocytes of animals with nucleated red cells. The red cell pipette is used, and a diluting fluid which conserves the red cells and shows up the white cells is necessary. For this purpose Toisson's fluid or physiological salt solution coloured with methylene blue may be used. The drawback to this procedure is that the large dilution does not give a sufficient number of white cells to yield a satisfactory average. This disadvantage may be minimised by using a counting chamber such as that of Zappert or Türk (Fig. 9).

Some practical points in connection with the counting of white cells may be noted. Unless one is dealing with a leucocythæmia the 1 in 10 dilution should always be used. The more leucocytes are counted the more nearly accurate is the result. Beginners should always repeat the count with a second drop, but with greater practice this becomes unnecessary. The settling of the whites on the ruled space takes a much longer time than that of the reds, and counting should not be attempted till it is complete, lest some corpuscles remain out of focus. If comparative counts are to be made on successive days, it is important

that this should be done as nearly as possible at the same hour and under the same conditions as regards rest and exercise, length of time after a meal, etc. The "standard" time is in the middle of the forenoon.

The Method of Measured Fields.—In this method the leucocytes are counted not in squares but in circular areas measured by the diameter of the microscopic field. The depth, $\frac{1}{10}$ mm., is determined by the Thoma counting chamber. Many different methods have been suggested. One of the simplest is that of Turton.[1] The cubic capacity of each quantity of fluid counted is $\frac{1}{100}$ c.cm. The diameter required to give this is practically $7\frac{1}{8}$ squares of the Thoma-Zeiss chamber. As every fifth square is divided, all that is necessary is to take a quarter of a half square along with seven whole squares to get the field required. Using a $\frac{1}{6}$-inch objective it is easy to arrange such a field by moving the draw-tube. The tube-length is noted and the field can then be immediately arranged at any time. Twenty fields may be counted. Suppose the dilution to be 1 in 20 and 70 leucocytes are seen. The average number in $\frac{1}{100}$ c.mm. will be 70 divided by 20.

$$\frac{70 \times 100 \times 20}{20} = 7000 \text{ per c.mm.}$$

Note that the addition of two cyphers to the number in twenty fields at once gives the number per cubic millimetre.

Bürker's Method.—Bürker's hæmocytometer is used as described on p. 10.

Strong and Seligman's Method.[2]—In this method a counting chamber is dispensed with. Five c.mm. of blood are mixed with 495 c.mm. of the following solution:—

Sodium chloride	0·75 grm.
Methyl violet	0·012 grm.
Formaline	1·5 c.cm.
Distilled water	to 100 c.cm.

Five c.mm. of this mixture are placed on a slide and allowed to dry. The actual number of leucocytes is counted by using a mechanical stage and an oblong diaphragm in the eye-piece.

The red cells may also be counted by adding 5 c.mm. of the first (methyl violet) dilution to 995 c.mm. of 8 per cent. solution of eosine. Five c.mm. of this are allowed to dry on a slide and the total number of red corpuscles is counted.

[1] *Brit. Med. Journ.*, 1905.
[2] *Brit. Med. Journ.*, 1903.

Enumeration of the Blood-Plates.—Some recent work has indicated that there are changes in the number of blood-plates corresponding to phases of disease, but it may be said that the enumeration of blood-plates does not yield results of clinical value in any way commensurate with the trouble involved. The chief difficulty is the great tendency of the plates to adhere to glass, and for this reason the use of pipettes has been criticised. Tschistowitsch,[1] however, obtained results by the use of the pipette and counting chamber apparently more accurate than without them. By the pipette and counting chamber method the procedure is the same as that for counting leucocytes, except that the diluting fluid is different. The following solutions may be employed :—

(1) Affanassiew's solution—

Sodium chloride . . .	0·8 grm.
Witte's peptone . . .	0·6 grm.
Distilled water . . .	100 c.c.
Methyl violet . . .	1 in 100,000.

(2) Pratt's solution—

Sodium metaphosphate (Merck) .	2 grms.
Sodium chloride . . .	0.9 grm.
Distilled water	100 c.c.

Another method is either to place a drop of preserving fluid on the skin before making a puncture, or to place a drop of preserving fluid on a slide and touch the drop of blood with the fluid. The red cells and plates are counted in a succession of fields and the proportion of plates to red cells is determined. The number of red cells per cubic millimetre is then counted in the ordinary way, and thus we may estimate the number of plates. Suitable fluids for this estimation, in addition to the above, are 1 per cent. osmic acid and equal parts of glycerine saturated with dahlia, and sodium chloride, 2 per cent.

We have obtained the best results by using Pratt's solution and ascertaining the proportion of plates to red corpuscles.

[1] *Folia Hæmatologica*, iv. 1907.

CHAPTER III

ESTIMATION OF HÆMOGLOBIN: THE COLOUR INDEX: CARE OF INSTRUMENTS

Estimation of Hæmoglobin.—The amount of hæmoglobin present in a unit of fluid is stated as a percentage of the amount in the same unit of healthy adult human blood. Numerous instruments for estimating the hæmoglobin percentage are available. They may be divided into two groups—

(1) Those in which a measured sample of blood is diluted until it matches a fixed standard.

(2) Those in which a measured sample of blood in fixed dilution is compared with a series of standards.

1. (a) *Gowers' Hæmoglobinometer.* — This instrument comprises a pipette to measure 20 c.mm. of blood, a tube containing a standard solution of picro-carmine in gelatine, a graduated tube for diluting the sample, and a bottle and dropper for distilled water.

Procedure. — A few drops of distilled water are placed in the graduated tube. Twenty c.mm. of blood are sucked up into the pipette and blown into the water in the graduated tube. The blood and water are gently shaken up to dissolve out the hæmoglobin. More water is now added by means of the dropper until the diluted blood matches the colour of the standard tube. It is not advisable to attempt accurate matching, but the mean point between under-dilution and over-dilution should be taken as the reading. The comparison should be made in daylight, unless the special tubes now supplied for use with artificial light are available. Both tubes should be held level with the eyes and against a white background. The position of the tubes should be transposed from time to time. The figures on the graduated tube indicate the percentage of hæmoglobin present. Healthy blood should, of course, retain a deeper colour than the standard till the mark 100 is reached. Blood deficient in hæmoglobin matches the standard before enough water to bring the solution up to the mark 100 has been added.

The instrument is cheap, simple, and sufficiently accurate, but the

standard tube is apt to fade in colour at a varying rate. At one time we made a series of observations with the same blood on a number of instruments which had been in use for some years, and found that the readings varied as much as 40 per cent.

(b) *Haldane's Hæmoglobinometer.*—This modification of Gowers' instrument has the following advantages :—

(1) The standard is a definite one, being a 1 per cent. solution of

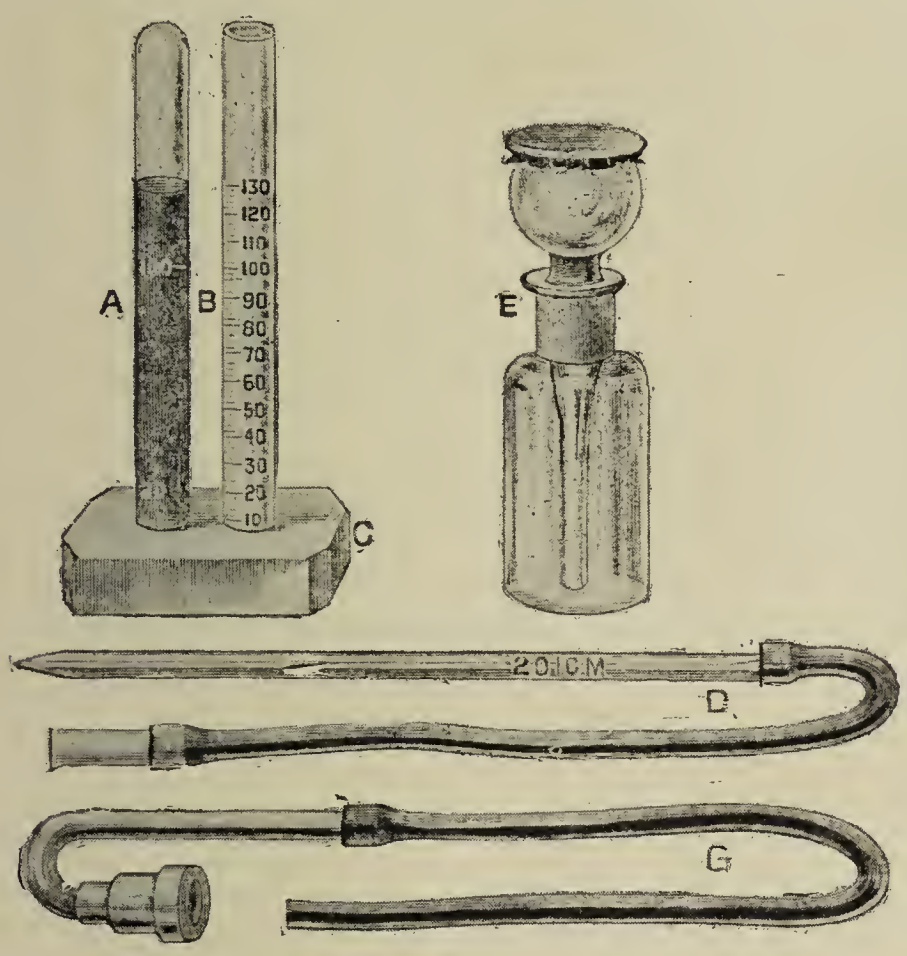


FIG. 13.—HALDANE'S HÆMOGLOBINOMETER.

A. The standard tube containing a solution of CO hæmoglobin. *B.* The graduated tube. *C.* The stand. *D.* The pipette. *E.* Drop bottle for distilled water. *G.* The connecting tube for gas.

blood containing the average amount of hæmoglobin in health saturated with carbon monoxide (CO). The solution should have an oxygen capacity of 18·5 per cent. as tested by the ferricyanide method. The standard may thus be tested at any time.

(2) The standard solution is permanent.

(3) The instrument may be used either by daylight or artificial light.

(4) The hæmoglobin to be determined is converted into CO hæmoglobin and a solution of this is tested against a CO hæmoglobin standard.

A limitation to the use of the instrument is the necessity for a convenient supply of coal gas.

Procedure.—The initial steps are the same as for Gowers' instru-

ment. Some water is first placed in the graduated tube, the blood is added, and then by means of a tube supplied with the apparatus the air in the graduated tube is replaced by coal gas from an ordinary burner. The end of the tube is closed with the finger and the tube is then inverted several times until the hæmoglobin is saturated with CO. More water is now added with the same precautions as for Gowers' instrument, and the mean between under-dilution and over-dilution taken as the reading.

(c) *Sahli's Hæmoglobinometer.*—The principle of this instrument is the same as that of Gowers'.

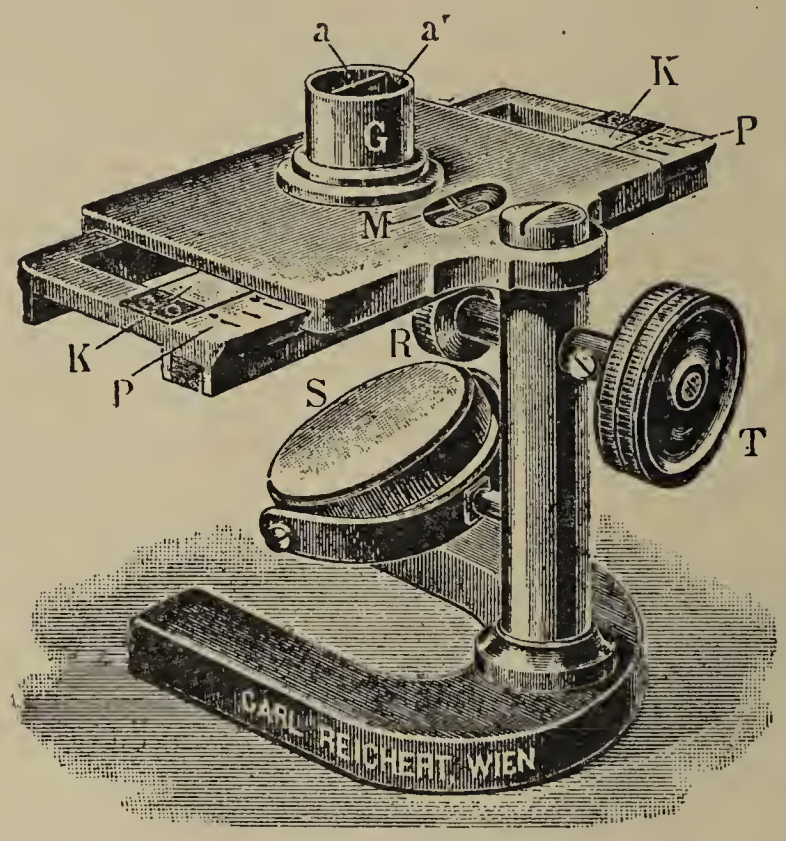


FIG. 14.—VON FLEISCHL'S HÆMOGLOBINOMETER.

G. The container. *a.* The compartment for diluted blood. *a'.* The compartment for distilled water. *K.* The glass wedge. *P.* The graduated scale. *T. R.* The rotating screw. *M.* The indicator. *S.* The reflecting surface.

The standard colour-tube contains a 1 per cent. solution of acid hæmatin. The graduated tube is filled up to the mark at 10 per cent. with decinormal hydrochloric acid. The blood to be examined is added to this acid, and in a few minutes its hæmoglobin is broken up and the pigment becomes acid hæmatin. We have now simply to dilute this specimen of acid hæmatin until it matches the acid hæmatin standard. The level of the fluid in the graduated tube indicates the percentage of hæmoglobin. The colour-tube is apt to deteriorate with age.

2. (a) *Von Fleischl's Hæmoglobinometer.*—This instrument consists of a cylindrical chamber divided into two compartments which is set over an aperture in a stage resembling that of a microscope.

Below the stage a wedge-shaped piece of coloured glass lies under one compartment and can be moved by a milled screw, so that any thickness can be brought under the compartment, the position of the wedge being indicated by a scale.

Light from a lamp is reflected from a white cardboard disc up through the wedge and the two compartments. A self-filling pipette mounted on a handle serves to collect and measure the sample of blood.

Procedure.—Half fill one compartment with distilled water. Dip the point of the pipette sideways into a drop of blood. Wipe its exterior. Plunge the pipette into the water in the compartment and wash out the blood. Now completely fill this compartment by adding water, and fill the other to be placed over the glass wedge with distilled water. Daylight being excluded, the observer takes such a position that the two compartments are divided vertically (right and left) and not horizontally. By means of the milled screw the position of the wedge of glass is altered until the colour in the two compartments is similar. In making the observation a series of glances should be employed and continuous staring avoided.

It is an advantage to look through a tube made of a roll of black paper. Use little light, and move the wedge with short, quick turns and not gradually. The reading is shown by the number on the scale opposite the indicator.

A diaphragm with an oblong slit crossing the two compartments may be employed to miminise the difficulty arising from the fact that the thickness of the wedge of glass and consequently the depth of colour varies in each field.

(b) *Fleischl-Miescher Hæmoglobinometer.*—This modification is essentially the same as the original Fleischl instrument. A pipette similar to that of Thoma is supplied for diluting the blood. It is graduated to give dilutions of one in either one, two, or three hundred. Two cells, one 15 and the other 12 mm. deep, are supplied in order that the observations may be controlled. The partition dividing the chamber projects to fit a groove in a cover-glass. A slotted diaphragm shuts off all but the central portion of the fields for comparison.

(c) *Oliver's Hæmometer.*—The principle of von Fleischl's apparatus is employed, but the standard is altered in a series of definite gradations. Oliver's instrument consists of a camera tube, a blood-cell and cover-glass, a series of circular standards in wooden blocks, and riders, a self-filling pipette, and a rubber-capped pipette with rubber tubing on its end for emptying the self-filling pipette.

Procedure.—Fill the measuring pipette with blood, wipe it, and immediately fit the rubber end of the capped pipette containing water

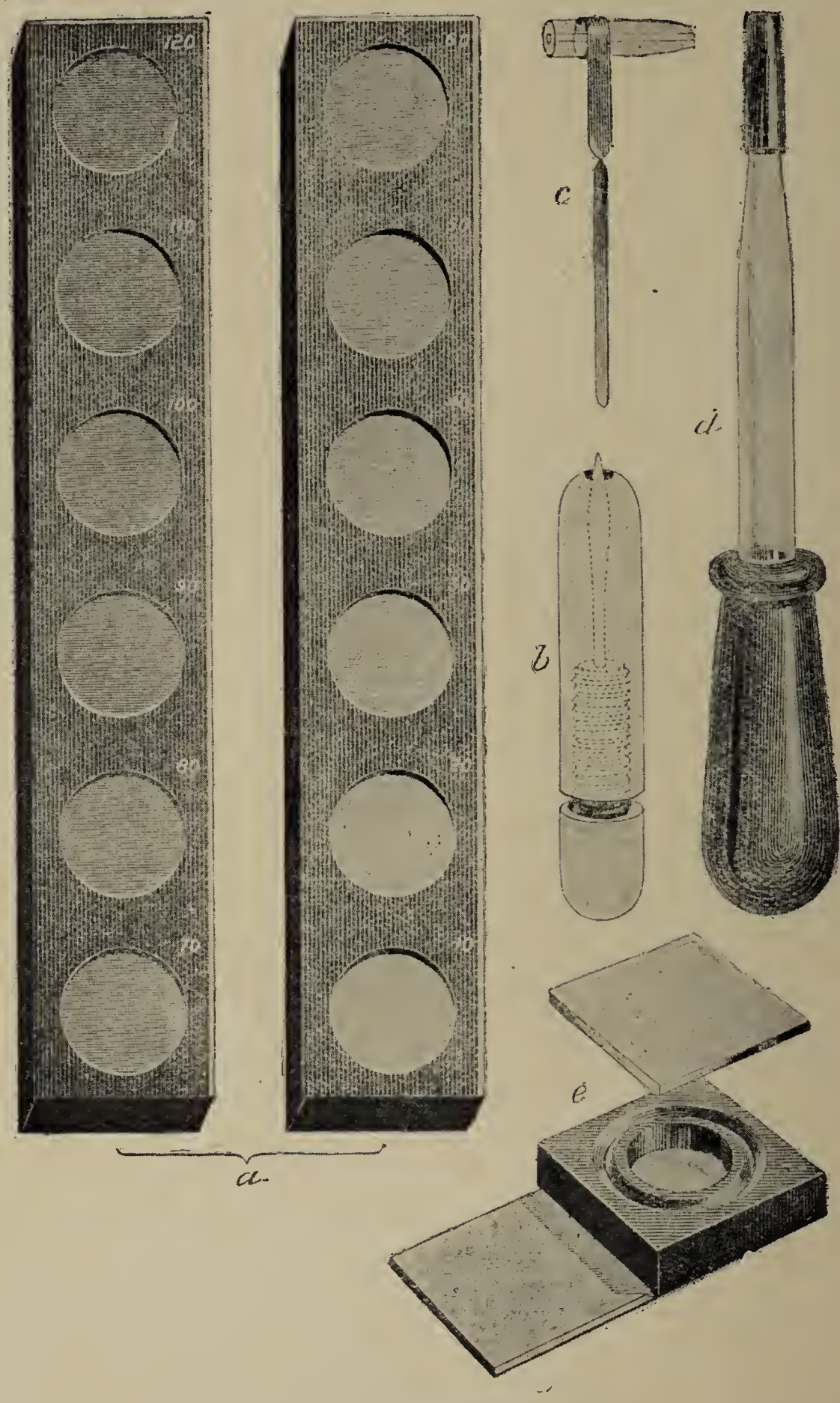


FIG. 15.—OLIVER'S HÆMOMETER.

a. The series of standard colour discs. *b*. Pricker. *c*. Self-filling measuring pipette. *d*. The diluting pipette. *e*. The blood chamber.

on to its pointed end, and wash out the blood into the cell. Add water, and stir with the handle of the measuring pipette till the blood-cell is full. Slide on the cover-glass. Note which standard approximately

matches the colour, and then compare more accurately by looking through the camera tube. It may be necessary to use a rider in order to secure accurate matching. The reading is indicated by numbers opposite each standard.

Two sets of standards are sold. One is for use by daylight, the

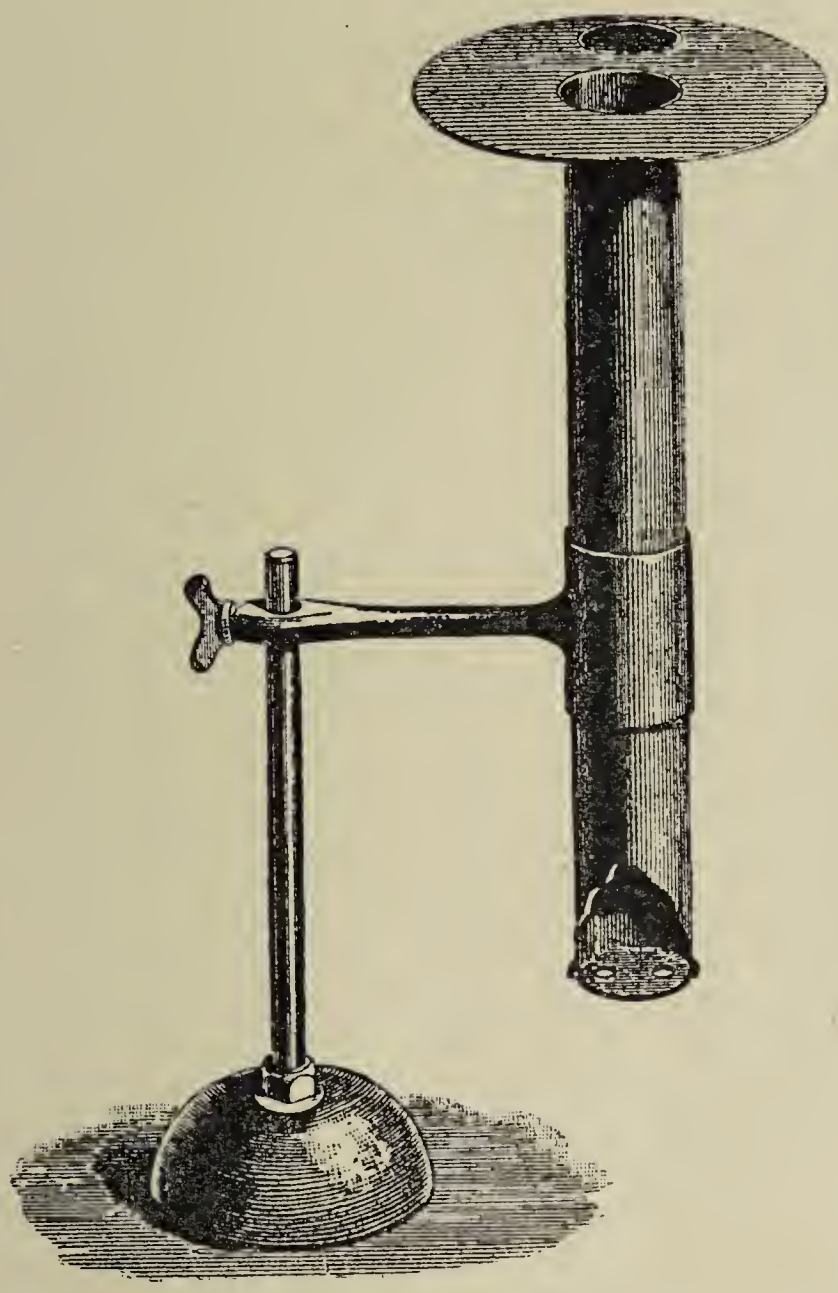


Fig. 16.—Camera Tube for Use with Oliver's Hæmometer.

other for artificial light. For the latter a Christmas tree candle is recommended.

(d) *Dare's Hæmoglobinometer.*—Undiluted blood is allowed to pass by capillarity into a slit between two little glass plates. The charged plates are then slipped into a window in the instrument beside a colour-prism. The reading is made through a telescope which magnifies the blood and the standard. The illumination is by candle-light, but the examination need not be carried out in a dark room. The standard colour-prism is rotated till the colours match and a knife edge indicates the result.

The instrument is expensive and fragile, and the examination must be made rapidly before clotting occurs, as this interferes greatly with the accuracy of the reading.

(e) *Tallqvist's Hæmoglobinometer.*—This has the advantage of great simplicity and is sufficiently accurate, with practice in using it, and control at first by other methods, for most clinical work. A drop of blood is allowed to fall on standard blotting-paper and the stain is matched against a series of colours on a lithographic scale, indicating from 10 to 100 per cent. of hæmoglobin. The tendency of beginners is always to read too high, partly because the colouring is based on von Fleischl's hæmoglobinometer, whose normal is 90 per cent.

(f) *Hall's Rotatory Hæmoglobinometer.*—The principle is the same as the above. The coloured standards are rotated till they match a blood stain.

The Ferrometer.—The amount of iron in blood may be estimated directly. The most simple apparatus for clinical use is the modification of Jolles' instrument made by Reichert. It is used in conjunction with the von Fleischl hæmoglobinometer.

Other Methods.—The hæmoglobinometers of Hayem and Malassez are not in common use. For a discussion of hæmoglobinometry and description of the chromophotometer and wedge-hæmoglobinometer, see Brugsch, *Folia Hæmatologica*, ix. 1 Teil, 1910, p. 201.

The Colour Index.—The colour index expresses the amount of the hæmoglobin complement per corpuscle. It is obtained by dividing the percentage of hæmoglobin by the percentage number of corpuscles as compared with blood containing 5,000,000 per c.mm. Thus the colour index in a person with 100 per cent. hæmoglobin and 5,000,000 red cells per c.mm., *i.e.* 100 per cent., would be unity. In the case of red cells, 2,500,000 and hæmoglobin 60 per cent. the colour index would be $\frac{60}{50} = 1{\cdot}2$.

The colour index is readily obtained by dividing the first three figures (or two figures when the number is under one million) of the blood count by five and then dividing the hæmoglobin percentage by the resulting number, or, what comes to the same thing, multiplying the first two figures of the count (or one figure when the number is under one million) by two and then dividing the hæmoglobin percentage by the resulting figure.

The colour index reaches its greatest height in cases of pernicious

anæmia, and the lowest indices are found in chlorosis. In secondary anæmia the colour index is generally less than one, but is seldom or never so low as in chlorosis. In very severe secondary anæmia the colour index is higher than in less serious cases.

Care of Instruments.—Scrupulous cleanliness is essential for the satisfactory use of the foregoing instruments. Especially is this the case regarding pipettes, and never under any circumstances should a pipette be put away dirty.

The short thick-walled pipettes of von Fleischl and Oliver's apparatus are readily cleaned by drawing a stout thread through them by means of a loop of fine wire, which should be entered at the pointed end.

Particular attention should be paid to pipettes of the Thoma-Zeiss type. Immediately after use the remaining fluid should be blown out, preferably in the case of the "red" pipette at least, through the wide end. Water should then be drawn through the pipette and blown out, and the process repeated a second time.

The same is next done with absolute alcohol and then with ether. The object of this is, firstly, to remove all albuminous material, and secondly, to leave the interior of the pipette thoroughly dry, so that when it is used again the diluted blood will advance evenly to fill the bulb. In cleaning the pipette it is very convenient to slip a tube attached to a rubber ball over its point. The fluids can then be more forcibly expelled, and all risk of blowing saliva into the pipettes is avoided.

If pipettes are not promptly cleaned a film which is not easily removed tends to form on their inner surface. This is more likely to occur in the case of the leucocyte pipette, and it is worth while from time to time to fill it with liquor potassæ and leave it for an hour or two. The softened and loosened film is then blown out through the wide end and the pipette is thereafter cleaned in the ordinary way. Another penalty of neglect is the precipitation of salts of Hayem's solution through evaporation at the point of the pipette. Prolonged soaking in water may be necessary to remove this deposit. If pipettes cannot be cleaned immediately after counting is finished, they should be placed in clean water to prevent evaporation and deposit, or closed at both ends with a rubber band as already described. Pipettes should, however, never be cleaned out until the observer is satisfied that his counts are correct, as it may be necessary to count a second drop.

A little clot readily forms at the extremity of the Thoma-Zeiss pipettes. If a pin or needle be used to remove this, the glass will almost certainly be chipped. A fine wire or a strong horse hair may be used carefully, but it is not an unknown accident for the wire to break, and then the last state of that pipette is worse than the first.

An obstinate clot may sometimes be got rid of by digesting it out with pepsin and hydrochloric acid.

The counting slide is to be cleaned with cold water, and occasionally washed with soap and cold water. Hot water, ether, and alcohol are not to be used, as they loosen the cement which keeps the ruled table and glass plates in place. Water is usually sufficient for the cover-glass, but it is none the worse for an occasional cleansing with soap and water followed by absolute alcohol.

CHAPTER IV

EXAMINATION OF STAINED FILMS—PROCEDURE AT THE BEDSIDE

Examination of Stained Films.—The importance of this method is as much under-estimated as the difficulties in carrying it out are over-rated. A well-prepared blood-film is a page of information to him who can read it, and in spite of assertions to the contrary we maintain that, in the great majority of cases, the experienced hæmatologist can tell from a good blood-film the number of red cells per c.mm. to within half a million, provided he knows the hæmoglobin percentage; and the number of leucocytes (unless they are markedly excessive) to within a thousand, especially if he has made the film himself. The films may be spread on either slides or cover-slips, and may either be treated while wet or allowed to dry before staining. We would urge the great importance of making well-spread films to work on. The staining of a mess of blood-clot or a clump of crushed and distorted blood-cells gives just the same satisfaction as developing a photographic plate which has been two or three times exposed. And just as the careful photographer can have his plates finished for him by the professional with results satisfactory to both, so he who doubts his hæmatological powers can easily obtain all the information a blood-picture can give by posting a good film to an expert.

Spreading the Film.—We much prefer the use of cover-slips. Their greater flexibility permits of more even spreading. They are more economical, inasmuch as less reagent is required, and where several samples are required they are less bulky and more easily stored.

Seven-eighth inch squares or circles should be used. Number 1 thickness is preferable for high-power work, but the beginner will perhaps be well advised to use number 2. *They Must be Clean.* Many elaborate formulæ for cleaning them have been proposed, but are unnecessary. If only a few covers are to be cleaned at one time, soap and water, followed by a rinsing in clean water, and drying with a clean, old, soft handkerchief, is all that is necessary. If a larger number are

wanted it is better to use nitric acid. This should be poured into a cylindrical urine glass and the covers allowed to drop one by one from the hand into it. They may be left for half a minute, then the nitric acid is poured back into the bottle, the urine glass filled with water, and with one hand over the mouth inverted and reinverted several times. The water is then poured away, and the washing repeated several times till all trace of the acid is gone. The covers are allowed to drain and then put into absolute alcohol, in which they may be left till required, or dried at once. It is not wise to dry too many at a time, as they become dusty very quickly. Glacial acetic acid, fluid soap, or lysol may be used instead of the nitric acid. The covers may be held in forceps or, provided only the edges are touched, between the finger and thumb.

A freshly exuded drop of blood is lightly touched with the centre of a cover-glass. The skin should not be touched. The charged cover-slip should then be allowed to drop on a second one and the blood will then spread out into a film. The cover-slips should immediately be slipped apart by a gliding movement, without either pressing or lifting.

Some practice is requisite in order to choose the moment when the exuding drop of blood is of the right size. If too large a quantity be taken up the cover-slips never come into close enough contact to spread a film, and if too small an amount be taken the cells may be distorted. A drop of suitable size should spread out to cover at least three-quarters of each cover-slip, with no heaping up of blood at one side, although in certain cases a small quantity of thickly smeared blood at one edge may be an advantage.

The cover-glasses are more easily slipped apart, when squares are used, if they are applied to each other so that the corners do not coincide, thus leaving projecting points of each free from contact with the other.

The films may either be allowed to dry or be treated by the wet method. For the former, films usually dry sufficiently rapidly without special manipulation. In a cold damp atmosphere they may be gently heated, and if held in the fingers rather than forceps the danger of overheating is very slight.

Films made on Slides.—A drop of blood is touched by a slide near its end, and the portion adhering to it may be either pushed along it by another slide with a rounded edge, so held that the drop of blood lies in an angle of 135°, or drawn along by a second slide, so held that the drop lies in an angle of 45° between the two slides.

Another method which has always seemed to us to have little to commend it is to touch a drop of blood with a cigarette paper or strip of gutta-percha tissue, apply this to a slide, and as soon as the blood has spread out to draw it along and off the slide.

The main disadvantage of these slide methods is that the larger leucocytes are carried out to the edges and end of the film, so that it is impossible to make an accurate differential count. They should not be used, therefore, for ordinary purposes, but are of use when a large quantity of blood is to be examined, as, for instance, in cases of malaria with few parasites, and in other parasitic diseases; but for these the method of thick dehæmoglobinised films is preferable (see Chap. XXXVII.).

Preparation of Dry Films—Fixation.—Such excellent and simple methods of combined fixation and staining are now available that a special paragraph on fixation is almost an anachronism, but in certain circumstances separate fixation is necessary. Its object is twofold—to conserve the hæmoglobin of the red cells, which would otherwise be dissolved out by watery staining solutions, and to fix the leucocyte granules.

Fixation by Heat.—This, the original method, has been given up for general purposes, but is still by far the best when Ehrlich's triple stain is to be used. When a steriliser is available, films may be heated to 110° C., and kept at that temperature for from ten minutes to an hour and then gradually allowed to cool. With the shorter exposure a heat of 120° C. does no harm. Cabot recommends rapid heating to 140° or 150° C., followed by rapid cooling. This last method gives occasionally very beautiful results, but is rather uncertain, the margin between over- and under-heating being narrow. Various small heaters consisting of a metal oven, thermometer and lamp are on the market. More simple heat fixation may be effected by passing the film from twelve to twenty times through a Bunsen or spirit flame, but the results are apt to be uncertain. The slow method is really the best.

Chemical Fixation.—The most useful methods are:—

(a) *Formol-Alcohol.*—Films are immersed for four minutes in a mixture of formaline 10 parts and absolute alcohol 90 parts, and are then washed in water and stained.

(b) *Alcohol and Ether.*—Films are placed in a mixture of equal parts of absolute alcohol and ether for half an hour. Longer fixation does no harm.

(c) *Formol Vapour.*—Films are exposed to the vapour under a bell-jar for from a half to one minute.

Staining of Dry Films

Very numerous methods are in vogue, and many possess special advantages. Ehrlich's triple stain has a time-honoured reputation for bringing out leucocyte granules, but it is now largely superseded by some of the eosine-methylene blue methods. The use of certain combinations of eosine and methylene blue results in the production of a blue colour in basophil cytoplasm and a violet or crimson colour in nuclei and some other structures—*Romanowsky effect.*[1] The red colour is not due to the direct effect of the eosine, though this dye at the same time colours oxyphil structures. The method brings out very full detail, and is exceedingly useful in the study of blood-parasites. The effect is obtained by the use of Giemsa's, Leishman's, and Pappenheim's methods described below.

The following account is by no means exhaustive:—The necessary manipulations are greatly facilitated by the use of Cornet's forceps to hold the cover-slips. A fairly efficient substitute is a wooden match with a split end and a notch to mark the loaded side of the cover-glass.

Eosine and Methylene Blue.—Fix in formol-alcohol for four minutes. Wash in water. Stain with saturated watery eosine for four minutes. Wash in water. Stain with saturated watery methylene blue for from thirty seconds to two minutes. Wash in water, dry, and mount in Canada balsam.

Red cells are stained pink; nuclei, blue; neutrophil granules, pink; eosinophil granules, scarlet; mast-cell granules, violet or crimson.

Giemsa's Stain—

Eosine, extra-höchst 0·5 per 1000 in distilled water	10 c.c.
Azur II., Grübler 0·8 per 1000 in distilled water .	1 c.c.

Fix films in absolute alcohol and stain for from fifteen to thirty minutes. Nuclear structure is well demonstrated. Mast-cell granules are stained a bright crimson.

Ehrlich's Triple Stain—

Saturated watery solution of orange G. .	14 c.c.
Saturated watery solution of acid fuchsin .	7 c.c.
Saturated watery solution of methyl green .	12·5 c.c.
Distilled water	15 c.c.
Absolute alcohol	15 c.c.

[1] For a useful discussion of Romanowsky staining see Scott, *Folia Hæmatologica*, xii. *Archiv*, 1911, pp. 302, 363. For an account of staining methods in general see Pappenheim, *Folia Hæmatologica*, ix. *Archiv*, 1910, p. 572.

Shake for some time, then add—

Absolute alcohol	10 c.c.
Glycerine	10 c.c.

These solutions are to be measured in the same vessel, without washing, mixed in the exact order given, but without shaking or stirring until after the first amount of alcohol has been added. At the end of the procedure the whole fluid should be thoroughly shaken up.

It is very much more satisfactory to buy this stain ready made, as a very slight deviation from the exact order given alters its properties. In making up the stain it is very important to be sure that the solutions of the stains used are really thoroughly saturated. The best results are obtained after fixation by heat. The films should be then stained for five minutes, washed rapidly in water, dried, preferably between layers of filter paper, and mounted in balsam. The red corpuscles should be stained orange, nuclei green, neutrophil granules a crimson-purple, eosinophil granules copper colour. Basophil granules are not stained, but appear in the cells as unstained vacuoles. The reason for this is that the basic stain used, methyl green, is a fairly exact chromatin stain, but not so basic as methylene blue, so that it has not the affinities of the latter stain for basophil protoplasm and basophil granules. Thus, lymphocyte protoplasm is stained pink. If the preparation has been overheated, no length of time of staining gives a satisfactory picture. The preparation looks as though it had been washed out too long, while with underheating the red corpuscles are pink or crimson instead of yellow, and nuclei are sometimes well stained, while the granules lack the sharp definition of a properly fixed specimen. It must be borne in mind that the nuclear staining by methyl green is not so deep as one is accustomed to in methylene blue preparations, except in the case of nucleated reds of normoblastic type, and in some polymorphs. Almost all other nuclei are of a faint greenish-blue. Fair results can also be got after fixing with formaline alcohol and formaline vapour, and even with alcohol and ether, but they are seldom so sharp as after heat. There is nothing in blood pictures which equals in beauty a good triacid specimen, but the stain is no longer used for general purposes. It is reserved for cases in which it is desired to bring out neutrophil granules, especially, for example, when one wishes to make a differential count of myelocytes and lymphocytes in myelocythæmia. It is a very satisfactory marrow stain, because of the large number of granular cells found there.

The name "triacid" which is sometimes applied to it is really a misnomer. There are two acid stains in it and one basic one, and presumably two neutral combinations also, although apparently the more powerful is that formed by the acid fuchsin and methyl green. The term "neutrophil" was originally applied by Ehrlich to the granules of the ordinary polymorphs because of their affinity for this neutral stain. The term triacid was given at first to a mixture of the three acid stains—indulin, nigrosin, and aurantia—which was devised by Ehrlich for eosinophil (acidophil) granules.

Hæmatein and Eosine.—Fix with a chemical fixative. Wash in water. Stain with hæmatein for five minutes or longer. Wash in water. Stain with saturated watery eosine for two minutes or longer. Wash in water, dry and mount. This procedure has the advantage of elasticity and can hardly be mismanaged. Nuclear structure is particularly well shown. Its disadvantages are that neutrophil granules are not stained, and it may be difficult to distinguish nucleated red cells from lymphocytes.

Heidenhain's Iron-Hæmatoxylin Method.—1. Fix films in formol-alcohol or in saturated solution of corrosive sublimate in 0·75 per cent. salt solution, then wash.

2. Place in a mordant of 2·5 grms. of ferric alum dissolved in 100 c.c. distilled water for three hours or longer.

3. Rinse in distilled water.

4. Stain for twelve hours or longer in equal parts of Weigert's hæmatoxylin and distilled water.

5. Rinse in tap water.

6. Replace in the iron solution to bleach and differentiate, checking the process by frequent examination under a low power.

7. Wash for ten minutes in tap water.

8. If desired, counter-stain with dilute watery eosine and wash.

9. Dry and mount.

This method requires too much time for ordinary use, but is of great service in demonstrating mitotic figures, granules, and centrosomes.

Combined Fixing and Staining Methods

Jenner's Method.—This stain is by far the most useful of all the methods. It is strictly a solution in methyl-alcohol of the eosinate of methylene blue, in an excess of methylene blue. The solvent used, which must be Merck's methyl-alcohol, pure for analysis and free from

acetone, has a special fixing action on red corpuscles, so great that the immersion of the film for half a minute or less suffices to fix them completely. The original method of making the stain, as published by Jenner, was unnecessarily tedious. Several firms of manufacturing chemists now make the stain in tablet form, the prescription being that one tablet shall be dissolved in 10 c.c. of methyl-alcohol. We have generally found that a better stain is made if two tablets are used to the same amount. Care must be taken that the bottle in which the stain is put be absolutely clean and dry. If larger quantities are required, however, it is easy to make the stain by the following prescription :—

> Of 0·5 grm. methylene blue (medic. rein) dissolved in 50 c.c. methyl-alcohol, take 25 c.c.
> Of 0·5 grm. water soluble eosine (yellowish) dissolved in 50 c.c. methyl-alcohol, take 20 c.c., mix, and add 20 c.c. of methyl-alcohol. This improves the keeping qualities of the solution, and does not weaken the stain.

The fluid is immediately ready for use, although it improves by being kept for twenty-four hours, and remains good for months if the bottle be kept tightly corked. If the methyl-alcohol be allowed to evaporate a precipitate is formed in the stain which spoils the preparations. The method of staining is to drop on the film, held in a pair of Cornet's forceps, five or six drops of fluid, enough to cover it thoroughly. After from thirty to sixty seconds the film is rapidly washed in distilled water until the edge becomes pink, and then allowed to dry in the air, being tilted on its side so that the lower edge of the cover drains into blotting-paper. Artificial heat must never be used to dry the film, as a certain amount of differentiation of the stain goes on in the slow drying, and it will be found that heated films are always too blue. The water used for washing out must be distilled; ordinary tap water removes the blue from the nuclei. One great advantage with this stain is that the result closely approximates to that obtained by successive staining with eosine and methylene blue, a method on which much of our nomenclature is based. It is also possible to bring out by it the special staining reactions of different cells and corpuscles. Thus a film stained in the way we have just described will show the reds of a greyish terra-cotta colour, the nuclei blue, the granules of neutrophil cells purple, those of eosinophils pink, and of basophils a deep blue purple, while blood-plates are pale blue, and all such details

as polychromasia and basophilia are properly brought out. On the other hand, if staining be prolonged for two or three minutes, or the time of washing be increased, the red part of the stain gains the upper hand, and therefore eosinophil granules can be brought out specially well in this way. But although nuclei continue to stain well, the finer gradations of polychromasia and basophil granules in the reds are apt to be lost. The commonest error in using this stain is to stain too long and wash out too much.

This stain is also very useful for marrow films, but should then be used in a rather different way. After staining for a minute with the original fluid, a few drops of distilled water should be dropped from a pipette on to the top of the fluid, with which it rapidly mixes. This mixture should be allowed to act for three minutes, and the film then placed in distilled water for three minutes more. This gives a better result in marrow films than any other method.

It is well known that films which have been kept longer than a month or two will not stain well with any of the methyl-alcohol fluids, but Jenner can be used to overcome this difficulty also. Fixing, in films which have been kept for a long time, is quite unnecessary, and indeed if Jenner be used alone with old films the result is that the dry plasma usually stains most energetically, the red corpuscles remain unstained, and very often the whites as well. If, however, a very dilute solution of Jenner in distilled water be made, say 20 or 30 drops to 1 oz. of distilled water, and the films allowed to remain in this for any time up to twenty-four hours, a very satisfactory differential staining can usually be obtained.

Leishman's Method.—The stain is a compound of alkaline medicinal methylene blue and eosine (extra B. A., Grübler). It is dissolved in pure methyl-alcohol in 0·15 per cent. solution.

1. Apply just enough stain to cover the film and leave it for two minutes.

2. Add drop by drop distilled or tap water till the solution and the film appear pink, then allow the diluted stain to act for three minutes.

3. Wash in distilled or tap water, dry (avoiding much heat), and mount in xylol balsam.

Red cells are pale pink, nuclei purple, neutrophil granules violet, eosinophil granules red, basophil granules dark blue or crimson, organisms and parasite bodies blue, parasite chromatin brilliant red.

Panchromic Methods

Pappenheim recommends a combination of Jenner's and Giemsa's method as bringing out the best possible results. The Jenner solution brings out the neutrophil and eosinophil granules, while the Giemsa stain intensifies mast-cell granules and defines nuclear structure.

The procedure is as follows :—

Dry films are fixed and stained in Jenner's solution for three minutes. Distilled water is then dropped on to the film till the stain acquires a pinkish colour. The dilute stain is allowed to act for three or four minutes; it is then washed off in distilled water and immediately followed by Giemsa's solution (3 drops in 2·3 c.cm. of distilled water). After five minutes the film is washed in distilled water, dried (not over a flame), and mounted.

Pappenheim's Panchromic Mixture.—More recently Pappenheim[1] has introduced a method which is intended to bring out in one preparation all the different affinities for basic and metachromatic dyes. Dry films are fixed for five minutes either in Jenner's stain or in equal parts of absolute methyl and ethyl alcohol. They are then stained for from five to ten minutes in 15 drops of the stain diluted in 10 c.cm. of distilled water. After drying in air the films are differentiated in a mixture of methyl-alcohol 3 parts and acetone 1 part.

The formula for the stain is :—

Methylene blue	1
Toluidin blue	0·5
Azur I.	1
Methylene violet	0·5
Eosine	0·75
Methyl-alcohol	250
Glycerine	200
Acetone	50

Wet Methods

1. Films are rapidly immersed, as soon as they have spread, into a fixing solution, and throughout the staining process must not be allowed to dry. Wet films may be fixed in formol-alcohol or corrosive sublimate solution and stained by any of the methods mentioned on pp. 30-32. After washing they are dehydrated in absolute alcohol, cleared in xylol, and mounted in balsam.

[1] *Folia Hæmatologica*, xi. 1 Teil, 1911, 194.

2. A simpler method[1] is as follows:—Films are plunged into a wide-mouthed bottle containing—

Saturated solution of eosine in absolute alcohol	25 c.c.
Pure ether	25 c.c.
Solution of corrosive sublimate in absolute alcohol (2 grms. in 10 c.c.) . . .	5 drops.

They are fixed in three minutes, but may be left for twenty-four hours. After thorough washing they are stained for a minute in saturated watery solution of methylene blue, washed in water, dehydrated with absolute alcohol, cleared in xylol, and mounted in xylol balsam.

Choice of Staining Methods.—For general use we unhesitatingly recommend Jenner's stain as the most suitable and convenient. Practically its only limitations are that it does not keep indefinitely and that it does not succeed without some trouble in staining old films. It is the ideal stain for one who is examining blood twice a week or more frequently.

Old films stained with Jenner have a dirty-green colour, which can sometimes be cleared up by soaking them for a night in distilled water.

For one who is not likely to examine films more often than once a month we recommend fixation in formol-alcohol, followed by eosine and methylene blue. We have stained films ten years old by this method with fair results.

For the demonstration of parasites Leishman's stain gives excellent results and is easily applied, but it is not so satisfactory for general purposes as Jenner. Neutrophil and eosinophil granules, polychromasia and basophilia, are not so well brought out.

For micro-photography iron-hæmatoxylin, hæmàtein and eosine, and Leishman's method are much superior to all the others.

Wet methods are only required for fine cytological work. Leucocytes are fixed as spherules and are not flattened out. Red corpuscles are always distorted, not so much because of the action of the fixing agent, as because they have been distorted in making the films, and have not time to return to their normal shape before fixation takes place.

In all cases some extra films should be made and held in reserve till a stained specimen has been examined. By so doing many vain regrets might be spared for patients who have left for another country or even another world before a new supply of films could be obtained.

[1] Gulland, *Brit. Med. Journ.*, 13th March 1897.

Procedure at the Bedside.—A great deal of unnecessary inconvenience is sometimes inflicted on patients in obtaining the blood for examination. A complete routine examination will include the examination of fresh and stained films, the enumeration of red and white cells, and the estimation of hæmoglobin. A certain amount of method will be a distinct advantage to observer and observed. The following articles are taken to the bedside and should be conveniently arranged upon a tray — a small table should be prepared for its reception :—(1) A pricker; (2) a well-washed linen cloth; (3) solution for conserving red corpuscles; (4) solution for white cells; (5) the hæmoglobinometer pipette; (6) the blood tube or chamber of the hæmoglobinometer containing a little distilled water; (7) the red corpuscle pipette; (8) the white cell pipette; (9) a microscopic slide; (10) an envelope bearing the patient's name and the date, and containing at least five clean cover-glasses.

A pair of forceps for manipulating cover-slips may be added if desired. The instruments are arranged to hand, the stoppers are removed from the bottles, and the slide and cover-slips are arranged on the envelope. The patient is asked to turn the head away from the observer. The lobule of the ear is rubbed with the cloth, which is then laid behind the ear. The puncture is made, and as a rule one puncture should be sufficient for the complete examination. The first drop of blood is wiped away. The hæmoglobinometer pipette is now filled, and the blood is blown out into the distilled water and gently shaken. The white cell and red cell pipettes are charged in succession and laid flat. A drop of blood is now taken up on a cover-slip, which is dropped on the slide. Films are made on the remaining cover-slips, and the procedure is complete. A fresh drop of blood should be used for each pipette and each pair of films. Light pressure is applied to the puncture for a few seconds. The films as soon as they are dry are placed in the envelope and the tray is removed.

CHAPTER V

SPECIAL METHODS OF EXAMINATION

A VARIETY of special methods may be required in certain cases.

The Viscosity of the Blood.—The viscosity of the blood depends mainly upon the number of corpuscles it contains. It is increased to an important extent when the number of red corpuscles is excessive. Many methods of estimating the viscosity have been suggested.[1] A simple apparatus is that of Denning and Watson.

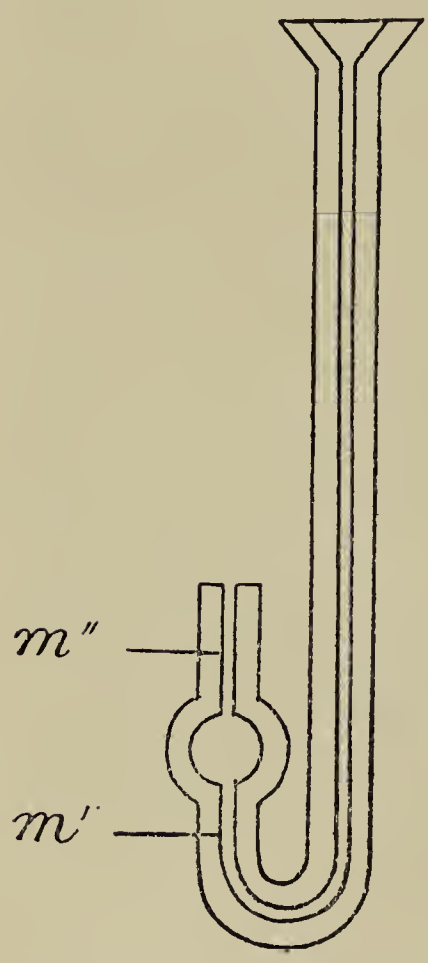


FIG. 17.—VISCOSIMETER OF DENNING AND WATSON.

The essential part of the instrument is a U-shaped capillary tube, with one arm about 6 cm. long and the other much shorter. The end of the long arm is expanded so as to be readily applied to the lobule of the ear; the short has a dilated bulb with a mark m' and m'' on either side of it. The instrument is applied to the ear vertically downwards, and the time taken for blood to flow from m' to m'' is noted, and compared with the time taken by distilled water. The apparatus supplied consists of six such tubes which differ in calibre, a stop-watch, and a pump and rubber tube for cleaning the pipettes or starting the flow of blood. If the blood to be examined is very fluid a pipette with a small bore should be selected; if the blood is unduly viscous a wide-bored tube should be chosen. The tube must be clean and must be at the same temperature as the patient when applied. The column of blood should be unbroken. If need be, the flow of blood may be started by applying suction to a rubber tube attached to the short arm. The time taken by the passage of distilled water and the time taken by the

[1] See *Folia Hæmatologica*, iv. 1907, 677 *et seq.*

blood sample is ascertained with the aid of the stop-watch. The result (obtained by dividing the water time by the blood time) is expressed as the ratio of the viscosity of blood to that of water.

Estimation of Coagulation Time.—In normal conditions the coagulation time is about three and a half minutes. Variations have been said to occur with the time of day, the amount of exercise, and the kind of food, but in an important paper Addis points out that these variations are much more likely to be due to variations in the temperature at which the observations are made. Contact between the blood and the tissues is an important factor. Lee and White[1] found that coagulation of blood drawn directly from a vein took place in an average time of six and a half minutes, while blood taken from a puncture in the ear clotted in three minutes. The coagulation time varies considerably in disease, but in only a few conditions is a knowledge of it of practical value. According to Addis the coagulation time is affected in bacterial diseases only when the organisms are present in the blood. Pneumococci and typhoid bacilli hasten coagulation, while staphylococci and streptococci delay it. In pneumonia there is no doubt that a rapid coagulation time is of ill omen.

Coagulation is manifestly delayed in hæmophilia, but shows no constant variation in most of the other blood diseases. Prolonged coagulation time is a serious feature in cases of pernicious anæmia. There is often delayed coagulation in jaundice.

While the amount of ionisable calcium in the blood can be increased by the oral administration of calcium salts and diminished by the administration of citric acid, Addis finds that the alteration brought about is less than that necessary to affect the time of coagulation.

1. *Method of Sabrazès and M'Gowan.*—This method was introduced by Sabrazès, and an almost identical method was described independently by M'Gowan three years later.

The exact moment of making a puncture is noted. The exuding blood is allowed to run into a capillary glass tube of 1·5 mm. bore. One end of the tube is then fused in a flame. This fusion keeps the column of blood steady, and care must be taken not to grasp the tube between the sealed end and the blood, otherwise the heat of the fingers and consequent expansion of air would lead to movement of the column. The tube is laid flat (preferably in a chamber kept at constant temperature), and at the end of every half minute a file mark is made on the

[1] *Amer. Journ. of Med. Sci.*, cxlv. 1911, p. 495.

glass tube about half an inch from the end of the column of blood, beginning at the end remote from the sealed portion of the tube. Each half inch is broken off. The glass ends are kept near each other and are then drawn apart. Whenever a thread of fibrin is seen between the ends the first stage of coagulation has occurred.

2. *Wright's Method.*—Blood is drawn into a series of tubes of equal calibre at definite intervals, and kept at constant temperature by means of a water bath. At varying intervals the observer blows through the tubes, and whenever blood cannot be expelled from one the "coagulation time" is taken.

3. *Buckmaster's Method.*—A drop of blood is taken up with a platinum loop and placed in an oven with glass windows. The loop is repeatedly turned from the vertical to the horizontal position and *vice versâ* by means of a handle outside, and the moment when the corpuscles are prevented from being affected by gravity by the formation of the fibrin network is noted.

4. *Addis' Method.*[1]—The apparatus is rather elaborate. Its great advantage is that the blood is kept at a definite temperature and treated in the same way throughout. A drop of blood is received on the end of a truncated glass cone, which is immediately placed in a special chamber on the stage of a microscope. This chamber is fitted with a thermometer and a tube with a nozzle, which discharges a stream of mineral lamp-oil kept at uniform temperature and flowing with uniform force, against the drop of blood. The nozzle is arranged so that it discharges the oil against the drop of blood tangentially, and thus keeps the corpuscles in constant movement without rotating the drop of blood as a whole. The corpuscles stream round and round for some seven minutes and then one or two stationary streaks appear. This streakiness rapidly spreads, and the end point is taken when there is the appearance of a clot and the cessation of movement of the great majority of the corpuscles. The coagulation time is the time which elapses between the puncture of the skin and this end point.

5. *Method of Lee and White.*—By means of an all-glass syringe 1 c.c. of blood is withdrawn from a vein in the arm and placed in a Widal test-tube. The tube is inverted every thirty seconds. The end point is taken when the blood ceases to flow or change its contour. The method lessens the accelerating effect on coagulation of contact with the tissues.

[1] *Quart. Journ. of Exper. Physiology*, i. 1908, 305. This paper contains a description of all the more important methods.

6. A method which gives fairly accurate results is simply to pass a needle through a drop of blood on a slide at intervals and note the time when a thread of fibrin is first drawn out.

7. Another method is to put a drop of blood on a slide and note when changes in contour cease on tilting the slide.

A quite satisfactory clinical procedure is to use one of the simpler methods without regard to temperature and examine the blood of a healthy person at the same time, expressing the result of the pathological blood as an index. The blood must be obtained in the same way in the two cases, and the amount of contact with foreign bodies must be the same.

The Alkalinity of the Blood.—The estimation of the alkalinity of the blood cannot be said to yield results which are of service in disease. The normal alkalinity is equivalent to about 0·3 per cent. of Na_2CO_3. It is increased during digestion and diminished after muscular exercise. It is greater in the early morning than later.

Practically all the statements made regarding the alkalinity of the blood in disease have been contradicted. There is a preponderance of opinion that alkalinity is diminished in the course of febrile diseases, and that successful antitoxin treatment in diphtheria and other diseases increases alkalinity. There seems a certain parallelism between the alkalinity of the blood and the body resistance.

The results hitherto obtained in the case of such diseases as diabetes, gout, rheumatism, and nephritis are hopelessly discordant.

1. *Rigler's Method.*[1]—A quantity of blood is placed in a flask containing 10 c.c. of absolute alcohol. The weight of the flask before and after the addition of the blood indicates the weight of the blood added.

The blood coagulates in the alcohol and is set aside for half an hour. At the end of this time 10 c.c. of distilled water is added, the mixture is shaken and again set aside for half an hour. Under these conditions the blood gives an alkaline reaction to the diluted alcohol.

Dilute sulphuric acid is now added drop by drop from a burette, and after each drop the reaction is tested with glazed red litmus paper. When the paper ceases to become blue the alcoholic solution is neutralised, and from the quantity of acid employed the alkalinity of the sample of blood is ascertained.

2. *Drouin's Method.*[2]—Two solutions are required—(*a*) Solution of

[1] *Central. f. Bakter.*, xxx., 13th December 1901.

[2] *Hémoalkalimètrie*, Thèse de Paris, 1892.

oxalic acid 2·1 parts per 1000; (*b*) solution of sulphate of soda 10 parts per 1000. In a series of ten test-tubes from right to left decreasing quantities of the acid solution and increasing quantities of soda sulphate are placed. The volume of the acid solution is thus kept constant.

Solution of oxalic acid .	10	9	8	7	6	5	4	3	2	1 drops.
Solution of sodium sulphate	1	2	3	4	5	6	7	8	9	10 „

Blood is collected in a graduated tube and placed in a known volume of saturated sodium sulphate solution to delay coagulation. Equal known quantities are now placed in each of the ten tubes.

The reaction in each tube is tested with glazed litmus paper. Those at the right will remain acid; those at the left will be alkaline; between the two one will be neutral.

The amount of acid in this tube indicates the alkalinity of the amount of blood added. The neutral sulphate of soda does not affect the result.

3. *Dare's Hæmoalkalimeter.*[1]—This method is based upon the disappearance of the spectrum of oxyhæmoglobin in the blood on neutralisation with a dilute solution of tartaric acid. The observation can be made with only a single drop of blood. The hæmoalkalimeter is a specially constructed tube.

4. *Precipitate Reaction Method.*—Boycott and Chisolm[2] point out that the colour of the indicator may vary materially with the presence or absence of protein. In the presence of protein the end reaction is therefore not well defined. These observers suggest a precipitate reaction as a test for the degree of alkalinity.

A series of small test-tubes are charged with quantities of N/1000 sulphuric acid, increasing by 0·1 c.c. from 0·0 to 1·2 c.c., the total volume of liquid in each tube being made up to 2 c.c. with distilled water. Each tube then receives a drop (about 0·02 c.c.) of blood, the contents are mixed, and the tubes are placed in a water bath at 45° C. for one hour. They are then wiped clean and examined. The tubes containing the smaller amounts of acid are very slightly opalescent. Those containing the larger quantities of acid show a flocculent precipitate. With normal blood this precipitate usually occurs in the tubes containing 0·7 and 0·9 c.c. of N/1000 acid. The end point is the point half way between the first tube which shows a precipitate, and the last which does not.

[1] *Bull. Johns Hopkins Hospital*, xiv. 1903, 175.
[2] *Biochemical Journ.*, v. 1910, 23.

A dropping pipette with an outside diameter of 1·2 mm. gives a drop of blood of rather more than 0·02 c.c. The exact volume for each experiment is obtained by weighing 5 or 10 drops and from the known specific gravity. Since the size of a drop of blood increases as coagulation becomes imminent, the drops should be distributed quickly. There is a difference in the size of the drop which the same pipette will deliver from the blood of different individuals even when all the samples show the same hæmoglobin content, but the variation in the case of blood showing the same percentage of hæmoglobin does not exceed 0·002 c.c., so that for many purposes, using a standardised pipette, weighing may be dispensed with. Knowing the volume of the drops, the amount of acid required may be expressed either in terms of a standard drop of 0·02 c.c. or as c.c. of N/10 acid per 100 c.c. of blood.

The end point is ultimately the same at whatever temperature between 15° and 45° C. the reaction takes place. The concentration of the acid and the volume are immaterial within wide limits, but comparison is facilitated by keeping them the same.

The precipitate is due to the presence of some part of the formed elements of the blood which does not go into solution when blood is laked with distilled water. The reaction is the same after as many leucocytes as possible have been removed. The precipitate is soluble in alkali and in excess of acid. The presumption is that the precipitate is composed of the nucleo-protein of the red cells. The characteristic flocculation is probably due to the presence of stromata.

Specific Gravity of the Blood.—(1) Mixtures of glycerine and water or solutions of various salts have been employed to provide a series of fluids of different specific gravity. These are placed in bottles and a drop of blood is added until it is found that the blood floats in one and sinks in another. The intermediate figure gives the specific gravity of the blood. These methods are unsatisfactory, because the blood diffuses into an ill-defined cloud, and in the glycerine mixtures it soon tends to sink even though it has been originally lighter than the fluid.

(2) *Hammerschlag's Method.*—This is a useful clinical method. A mixture of chloroform and benzole of a specific gravity of 1055-1060 is made. A drop of blood is allowed to fall into this from a pipette. If the drop sinks, chloroform must be added to the mixture; if the drop floats, benzole should be added and the mixture stirred with a glass rod.

When the drop remains suspended, with no tendency either to sink or to float, the mixture has the same specific gravity as the blood. The specific gravity is then ascertained by means of a sensitive hydrometer.

(3) *Whyte's Method.*[1]—Whyte obtained the most satisfactory results with a mixture of oil of wintergreen (*i.e.* methyl-salicylate, sp. gr. 1·180) and castor oil (sp. gr. 0·950). In this the blood remains as a definite globular drop, which will *keep* floating at the surface of a mixture of higher specific gravity, and will definitely sink to the bottom in a mixture of lower specific gravity. The examination is rapidly made at the patient's bedside if bottles of the testing mixture are prepared beforehand representing the different specific gravities desired—a plan which cannot be carried out if chloroform and benzole are employed, on account of their extreme volatility.

In the use of this oil mixture two points must be noted: in the first place, a drop not smaller than 5 c.mm. should be employed, as, if the specific gravities of the blood and the oil do not differ greatly, drops smaller than this will neither rise nor fall, but, owing to the friction of the fluids, will remain stationary.

In the second place, the heavier ingredient of the mixture (the oil of wintergreen) is more volatile than the lighter, so that, if the bottle is frequently opened, the specific gravity of the mixture will become appreciably lower after a few days; in any case, however, a new supply of oil will be required by that time on account of the accumulation of blood-drops in the testing fluid. In the case of the glycerine and water mixture there exists the same need for a fresh supply at frequent intervals, owing to the increasing turbidity produced by the repeated addition of blood-drops. This method is more rapid than Hammerschlag's, and is therefore very useful when frequent estimations are required.

The important effect of *temperature* upon specific gravity must be borne in mind in the preparation of these mixtures for testing the blood. The contents of a specific gravity bottle may weigh 1000 grains in the temperate climate of Europe, and only 997 grains during the hot season in the tropics. The same difference of specific gravity will be shown if a hydrometer is used.

The normal specific gravity is about 1055. It varies in direct proportion to the amount of hæmoglobin in the blood.

The Molecular Concentration of the Blood—Cryoscopy.—This

[1] Edinburgh thesis (unpublished).

method depends upon the fact that the freezing-point of water is lowered by substances in solution in direct proportion to the number of molecules and ions in solution.

Beckmann's cryoscope is most commonly used. It consists of a covered glass jar (*C*) which contains the freezing mixture and stirrer (*E*) which projects through the cover. In a central aperture in the cover there is fixed a wide test-tube (*B*). In this test-tube is a cork which supports the freezing tube (*A*). The freezing tube has a side opening, and contains a delicate thermometer (*D*) and a stirrer (*F*) made of platinum wire.

As the thermometer has not a fixed zero, the reading which it gives for distilled water must first be ascertained. The bulb of the thermometer is fully submerged in distilled water, the outer chamber is filled with a freezing mixture. The freezing tube may at first be placed in the freezing mixture, but after it has cooled to near the freezing-point it must be transferred to tube *B*, where it will be protected from the freezing mixture by a covering of air. As the water gradually cools it reaches a temperature rather below its true freezing-point and then freezes. If freezing be unduly delayed it may be induced by dropping a minute particle of ice through the side opening of the freezing chamber. At the moment of freezing the latent heat of ice is liberated and the temperature again rises and remains up for a short time. At this point the temperature is taken. The process is then repeated with blood instead of distilled water.

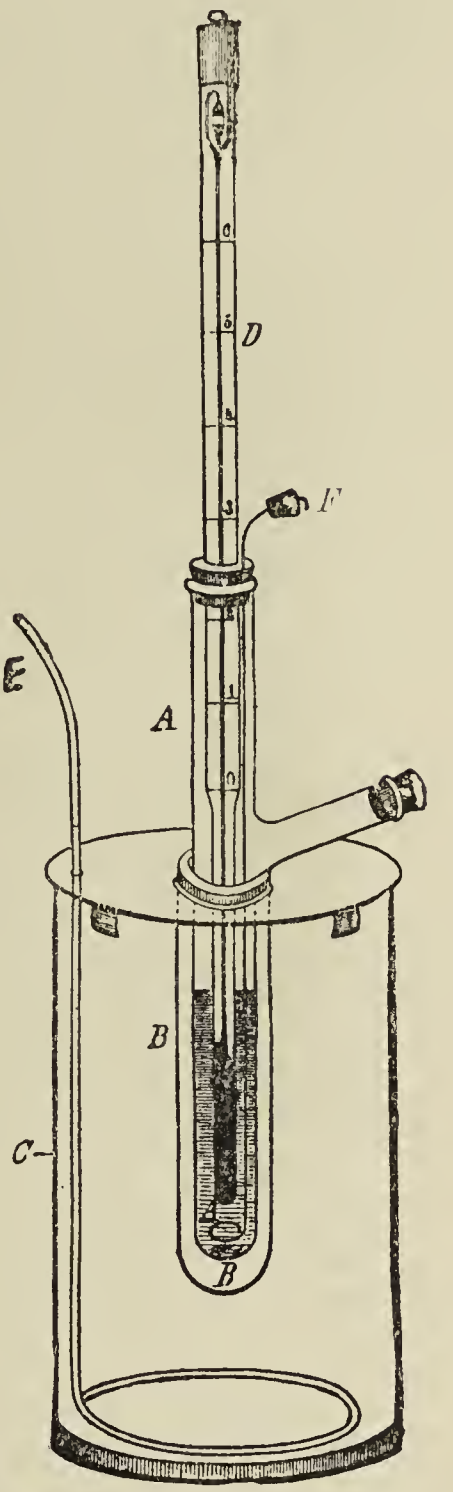


FIG. 18.—BECKMANN'S CRYOSCOPE.

A. Freezing tube. *B*. Supporting tube. *C*. Container for freezing mixture. *D*. Thermometer. *E*. and *F*. Stirrers.

Normally, the depression of the freezing-point by the substances in blood is 0·56° C. The lowering in degrees centigrade is expressed by the term Δ.

The Δ of 0·95 per cent. solution of NaCl is also 0·56° C. Such a solution is isotonic with blood.

The Δ of any solution may be expressed in terms of a gramme-molecular solution (1 grm. × the molecular weight of the substance is dissolved in 100 c.c. of water) by dividing it by 1·87, since a gramme-molecular solution of a non-electrolyte (a substance incapable of becoming split up into ions in solution) is known to lower the freezing-point 1·87° C.

For example, if the Δ of blood be 0·56° C., then

$$\frac{0{\cdot}56}{1{\cdot}87} = 0.3.$$

The blood therefore contains 0·3 gramme-molecules in 100 c.c.

In carrying out a cryoscopic examination the freezing mixture may be ordinary salt and ice, but for accurate results the freezing mixture should be composed so that it is only slightly colder than the freezing-point expected in the substance under examination.

Certain salts give a constant temperature when mixed with a smaller quantity of ice. These have been tabulated by Cohen.

A few examples are:—

Sodium sulphate	0·7° C.
Potassium chromate	1·0 „
Potassium sulphate	1·5 „
Potassium nitrate	3·0 „
Zinc sulphate	5·0 „

A depression of the freezing-point of blood greater than 0·58° C. indicates inadequate kidney function.

Fragility of the Red Corpuscles.—The resistance of the red corpuscles to lysis by dilute solution of salts is sometimes a matter of some diagnostic significance. The resistance is definitely lowered in congenital family cholæmia and is increased in obstructive jaundice.

Process.—The corpuscles should be washed by centrifuging a small quantity of blood in 0·85 per cent. salt solution. A one per cent. solution of salt is diluted with distilled water in different proportions, *e.g.* one part with nine parts, two parts with eight, three with seven, and so on. The resulting 0·9, 0·8, 0·7 and more dilute solutions are placed in a series of small test-tubes and a roughly similar amount of the suspension of corpuscles is added to each. The tubes are inverted once or twice to mix the contents and left for an hour. Hæmolysis is indicated by a red tingeing of the solution, and its absence is indicated by a precipitate of the corpuscles while the solution remains colourless. In normal conditions hæmolysis does not occur with salt solutions stronger than 0·4 per cent. It has been shown that resistance of the corpuscles to hypotonic solutions is not necessarily proportionate to their resistance

to saponin or other hæmolytic agents. (See M'Neil, *Journ. of Path. and Bact.*, xv. 1910, p. 56.)

The Total Quantity of Blood in the Body.—A method applicable to the human subject has been suggested by Haldane and Lorrain Smith [1]—

1. The percentage oxygen (or carbon monoxide) capacity of the patient's blood, *i.e.* the capacity of 100 c.c. of blood for O or CO, is determined by testing a sample against standardised ox blood.

2. The subject under observation then inhales a measured volume of CO. The percentage saturation of the blood by this quantity is determined by the carmine method,[2] and the total oxygen (or CO) capacity is deduced.

Suppose the percentage O capacity be 20 and the total O capacity be 600 c.c., the total volume of blood would be

$$600 \times \frac{100}{20} = 3000 \text{ c.c.}$$

The latter figure multiplied by the specific gravity of the blood will give the total quantity of the blood in grammes.

Lorrain Smith [3] has found that in chlorosis there is an increase of plasma, and that in pernicious anæmia the amount varies.

Unfortunately in many cases in which the method would give useful information it appears to be not without danger.

Bacteriological Examination of the Blood.—In typhoid fever and certain other conditions micro-organisms may be found with fair frequency in stained films.

The presence of organisms is determined with much greater certainty by making cultures. Blood is withdrawn from a vein in the forearm. A wide area round the vein selected should be scrubbed with soap and water, then dried with a towel, and afterwards rubbed with methylated spirit on sterilised wool. Finally, some ether is poured on the part and allowed to evaporate. The syringe to be employed should be capable of being boiled, and its capacity should be about 10 c.c. It is boiled with the needle in position for ten minutes in a 1 per cent. solution of potassium citrate. Two tubes each containing about 20 c.c. of broth and two sloped agar tubes should be at hand.

[1] *Journ. of Physiology*, xxv. 1900.
[2] *Journ. of Physiology*, xxii.
[3] *Trans. Path. Soc. London*, 1900, 311.

A bandage is wound round the upper arm to constrict the veins. About 1 c.c. of the potassium citrate solution is drawn into the syringe to delay coagulation, the needle is inserted downwards into the vein, and by very gently withdrawing the piston blood is allowed to flow into the syringe. At least 5 c.c. should be obtained if possible.

Two cubic centimetres are placed in each tube of broth and gently shaken up. A quantum of the remaining blood should be allowed to trickle over the surface of the agar in the remaining tubes.

For further procedure a work on bacteriology must be consulted.

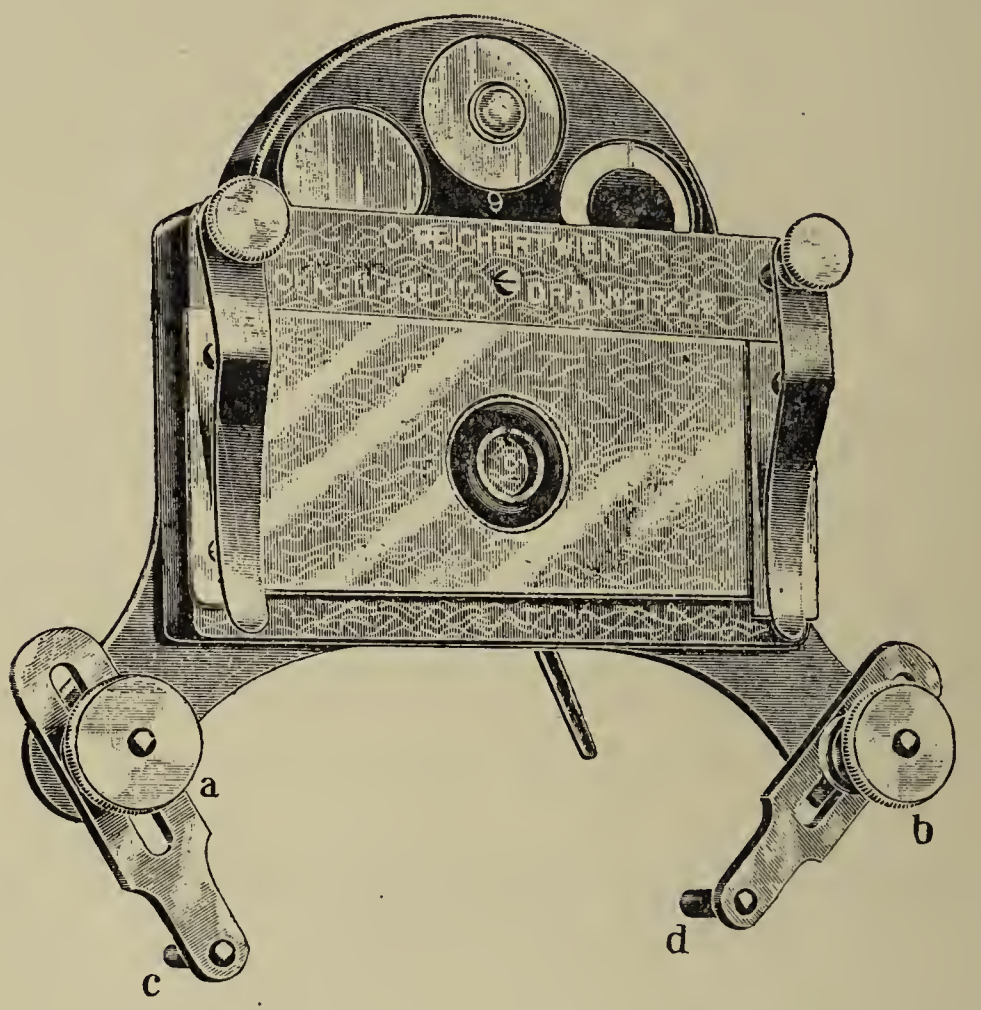


Fig. 19.—Reichert's Universal Condenser.

Dark-ground Illumination.—By means of a reflecting condenser the direct rays from the illuminant are not allowed to enter the objective.

The result is a brilliant illumination of the objects on which the light is focussed while the ground is kept dark.

The method brings into view "ultramicroscopic" objects such as fatty particles in blood plasma which are not made visible by transmitted light. Leucocyte granules are clearly demonstrated, and such fine objects as the spirochæta pallida can be shown without special preparation, even with dry high-power lenses. While the method does not supersede the use of stains which bring out details depending on tinctorial

affinities it is a valuable adjunct to our resources. Differential leucocyte counts for ordinary routine diagnosis can be made from fresh specimens, but in such conditions as leukæmia, where tinctorial distinctions are essential, the method is not available. The method has added considerably to our knowledge of erythrocyte structure, and has demonstrated the real existence of objects which might have been regarded as staining artefacts. Different patterns of reflecting condensers are on the market. These usually take the form of either a sub-stage lens which replaces the Abbe condenser, or a plate condenser which lies on the stage of the microscope.

Of the latter class Reichert supplies a very convenient pattern. Under the reflecting lens is a wheel diaphragm which carries a number of stops of different size, a ground-glass disc, and a plano-convex lens. The latter, together with the reflecting lens, performs the functions of an Abbe condenser, so that by merely turning the wheel objects can be viewed either by reflected or transmitted light in rapid succession.

Oil-immersion lenses for use with reflecting condensers should be fitted with a conical groove to reduce the numerical aperture to 1·0.

The Glycogen Reaction.[1]—In certain conditions many of the polymorphonuclear leucocytes contain glycogen in their protoplasm. Its occurrence may be of considerable diagnostic significance.

The method is simple. The following solution is required:—

Iodine	1 grm.
Iodide of potassium	3 grms.
Distilled water	100 c.c.

With enough gum acacia or gum arabic added to make the fluid of a syrupy consistency.

A large drop of this fluid is placed on a slide, and a cover-slip bearing the dry film to be examined is lowered on to it. After half a minute the cover-slip is pressed down and the surplus fluid is wiped off. The film is in this way fixed, stained, and mounted, and the preparation lasts for some days.

The examination should be made with an oil-immersion lens in good light, daylight being preferable. If artificial light be used it should be as white as possible, that from an incandescent gas burner being satisfactory.

A film of normal blood treated in this way shows the red cells stained yellow on a white or pale yellow background, the white cells

[1] See Gulland, *Brit. Med. Journ.*, 16th April 1904.

being more faintly stained than the red corpuscles. Lymphocytes are not readily distinguished. The polymorphonuclears look darker because of their closely-set granules, while eosinophils are readily recognised by the high refractive index of their granules. A brown or reddish-brown colour may be seen in some of the masses of blood-plates but not in any of the cells. The amount of this extra-cellular glycogen varies greatly. It seems uniformly increased in diabetes, but in other conditions it follows no ascertained law and is therefore disregarded.

When the reaction is "positive" the change occurs in the polymorphs alone, except in rare cases of myelocythæmia, in which glycogen appears in basophils and myelocytes. The polymorphs may show the reaction in three ways—(1) as a diffuse colouration (Plate I., 4); (2) as fine granules scattered through the whole or part of the cell body (Plate I., 5, 6); (3) as coarse granules or masses which may be scattered throughout the cell body but are more usually found at or near the periphery, sometimes projecting as pseudopodia. The latter are only seen when the reaction is well marked (Plate I., 7, 8). The granules are quite distinct from the neutrophil granules, and are never seen in the nucleus.

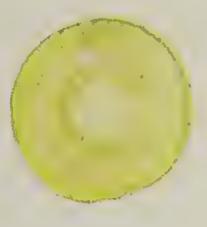
The conditions under which the reaction occurs are—

1. Severe disturbance of respiration.
2. Anæmia, though only in such cases that it is doubtful whether the anæmia *per se* has anything to do with the reaction.
3. Toxæmias of metabolic origin (uræmia, chronic morphinism, malignant cachexia, etc.).
4. Suppuration and bacterial infection.

Only those cases of diphtheria which are associated with much inflammation give the reaction. In typhoid it is never intense, and only appears at the end of the second week. The chief clinical conditions in which the reaction is positive and of diagnostic importance are pneumonia, empyema, lung gangrene, septicæmia and all advancing suppurative processes, septic gangrene, appendicitis, and peritonitis.

It may be of use in distinguishing gonorrhœal arthritis from rheumatism, cerebral abscess from cerebral tumour, and in many such circumstances. The reaction denotes a serious condition.

The Oxydase Reaction.—This reaction depends on the oxidising power of certain leucocytes. Pus or blood containing numerous granular leucocytes will bring out a blue colour when added to tincture of guaiac without the addition of peroxide of hydrogen. As the guaiac-



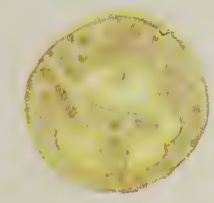
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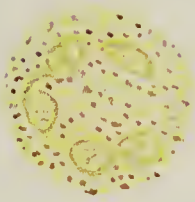
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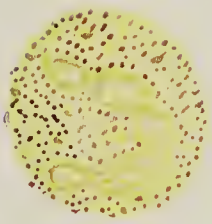
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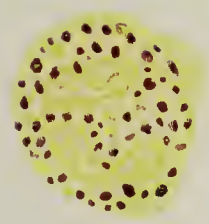
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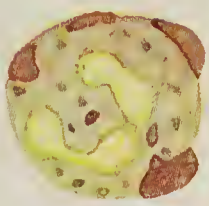
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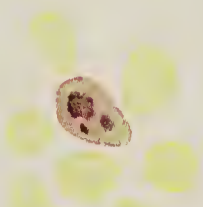
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Plate I.—The Glycogen Reaction.

1. Normal erythrocyte.
2. Normal large lymphocyte.
3. Normal polymorphonuclear neutrophil.
4. Diffuse glycogen reaction.

5, 6. Finely granular glycogen reaction.

7. 8. Coarsely granular glycogen reaction.

9. Extracellular glycogen and blood-plates.

G. L. G., *fecit.*

blue does not develop if the leucocytes have previously been boiled, it is assumed that the oxidising agent is a ferment. The microscopic test depends on the production by the action of oxygen of an insoluble dye from two soluble substances. When α-naphthol and dimethyl-para-phenylendiamin are brought together in an alkaline medium they become oxidised and form a blue dye-stuff, indophenol blue, which is precipitated. The presence of an oxidising agent accelerates the reaction, and the oxidising ferment of leucocytes brings it about with great rapidity, so that the blue dye is precipitated on their protoplasm. The reaction is given by eosinophil, neutrophil, and basophil leucocytes, and by myelocytes in marrow and leukæmic blood. According to Dunn it is also given by large hyaline leucocytes in normal blood and by myeloblasts of a late type, but it is not given by early embryonic myeloblasts. The reaction is not given by lymphocytes (other than large hyaline cells) or red corpuscles. The only adult tissues which give it are bone-marrow and the epithelium of the parotid and lachrymal glands. Otherwise it is found only in granular leucocytes in the vessels. It is not given by tissue basophils (Pappenheim and Nakano). The reaction is thus of great value in showing the distribution of myeloid tissue in fœtal organs, and of myeloid deposits in the organs in cases of leukæmia. It has also been employed to assist in distinguishing between cases of lymphatic (lymphocyte) and myeloblast leukæmias. Its significance in this connection is discussed in the chapters on these conditions.

Process.—Fixation by formol, osmic acid 1 per cent., or alcohol, does not affect the reaction, and Dunn has shown that tissues will show it after they have been embedded and cut in paraffin, but the freezing method is usually employed. Blood films may be fixed for five minutes in formol vapour. There are several methods of carrying out the actual test.

I. *Schultze's Method A*—

Solution 1. α-naphthol, 1 grm.
Distilled water 100 c.c. heated just to boiling point.
Liquor potassæ 1 c.c. added drop by drop.
Solution 2. One per cent. watery solution of dimethyl-para-phenylendiamin.

II. *Pappenheim's Method*—

Solution 1. α-naphthol 1 grm.
Absolute alcohol 30 c.c.

Distilled water 100 c.c.
Strong ammonia 3 drops.
Solution 2. Para-phenylendiamin 1 per cent.

The solutions for these methods should not be new. Films or sections are treated with the solutions in succession.

III. *Schultze's Method B*—

Solution 1. Two per cent. watery solution of β-naphthol-natrium (=mikrozidin, Merck).
Solution 2. One per cent. solution of dimethyl-para-phenylendiamin hydrochloride.

IV. *V. Gierke's Method*—

Solution 1. α-naphthol 1 grm. dissolved in 100 c.c. boiling physiological salt solution and filtered.
Solution 2. One per cent. watery solution of dimethyl-para-phenylendiamin.

The solutions for these two methods should be fresh, and are mixed before use. Specimens are treated with the mixture.

Nakano has recently studied the different methods, and finds that the eosinophil granules are easily stained by the first two, while the latter are preferable for neutrophil cells. The two latter methods are more sensitive and more labile than the first two. Gierke's is the best for formol material. Unfixed preparations last only about four hours. Fixed specimens last about twenty-four hours, but faded specimens can be stained again and again. As the indophenol is rapidly soluble in alcohol and xylol, specimens cannot be mounted in balsam with the exception of those prepared by Pappenheim's method. Dunn recommends undiluted water-glass as a mounting medium.

Fatty Degeneration of the Blood Cells.—Films may be fixed in formaline vapour for fifteen minutes or longer and stained with Sudan III. or scharlach R. Shattock and Dudgeon[1] recommend a saturated solution of scharlach R. in 75 per cent. alcohol. After staining, the films are washed in 75 per cent. alcohol, then water, and may be counter-stained with hæmalum for three minutes, washed, and mounted in Farrant's medium. Fat is found in the leucocytes in a variety of toxic and chronic conditions. In diphtheria and pernicious anæmia a scharlach granulation not quite identical with fat has been described.

Vital Staining.—Two methods are available—(1) A dilute solution

[1] *Proc. Roy. Soc.*, 1907.

of the stain in physiological salt solution is placed on the skin before a puncture is made. The puncture is made through the drop of staining fluid and the exuding blood immediately comes in contact with it. Films are made from the mixture in the ordinary way. (2) Cover-slips are charged with the stain in a dry condition. This is effected by applying a drop of an alcoholic solution of the stain (0·02 grm. stain in 20 grms. alcohol) and allowing it to evaporate to dryness. A prepared cover-slip is charged with a drop of blood, a second clean cover-slip is dropped upon it, and after two or three minutes the cover-slips are drawn apart and the films are allowed to dry. The most useful stains are neutral red, azur, and methylene blue.

After vital staining films may be fixed and stained by other methods.

In addition to the granular basophilia, which may be seen in red cells in certain conditions, the vital method demonstrates a filamentous substance and also metachromatic granules in the erythrocytes. (See *Folia Hæmatologica*, 1907, supplement Hefte, 1 *et seq.*)

Estimation of the Calcium Content of the Blood.—This method was introduced by Blair Bell,[1] who considers that calcium salts play an important part in connection with the reproductive functions in the female. The method consists in the conversion of the lime into calcium oxalate and the enumeration of the oxalate crystals.

By means of a special pipette 100 c.mm. of blood are added to a glass capsule containing 250 c.mm. of a 1 in 30 aqueous solution of oxalic acid. The neck of the capsule is then sealed and the contents are thoroughly shaken. Thereafter 250 c.mm. of the following mixture are added:—

Acetic acid 1 per cent. . . .	95 parts.
Glycerine	5 „

After standing for ten minutes 100 c.mm. of this mixture are added to 500 c.mm. of distilled water. The crystals of calcium oxalate in this dilution are now counted by means of the hæmocytometer.

[1] *Brit. Med. Journ.*, 20th April 1907.

PART II

THE FORMED ELEMENTS OF THE BLOOD

CHAPTER VI

THE ERYTHROCYTES

Under the microscope a drop of blood is seen to contain numerous cellular bodies—the erythrocytes or red corpuscles and the leucocytes or white cells—as well as certain other elements—the blood-plates and "blood dust."

The Erythrocytes

(*a*) **Colour.**—In a fresh drop of blood the erythrocytes have a pale yellow colour when seen singly; masses of erythrocytes appear red.

(*b*) **Size.**—The average size of the red corpuscles is 0·0075 mm. (7·5 micromillimetres or μ). The size shows very little variation in health. The average size, however, is considerably reduced in the case of the inhabitants of high altitudes.

Pathological Variations.—In all anæmic conditions of any severity the corpuscles show inequality of size (anisocytosis). Usually the average diameter is diminished, but in pernicious anæmia a large number of specially large cells (megalocytes) appear, consequently the average size is increased.

(*c*) **Shape.**—In man and all other mammals except the *Camelidæ* (which have oval and biconvex corpuscles) the erythrocytes appear in ordinary preparations as biconcave discs. The centre of each disc shows a clear area, which is very conspicuous in stained specimens. Its proportion to the rest of the cell is an important guide in the estimation of the severity of anæmic conditions.

Weidenreich[1] maintains that the red blood corpuscles of mammals are bell-shaped and not biconcave until deformed by extraneous influences. This observation is supported by Lewis,[2] who finds that the corpuscles as seen in

[1] Weidenreich, *Arch. f. mikr. Anat.*, Bd. lxi. 1902, 459.

[2] Lewis, *Journ. of Med. Research*, January 1904. See also Orsós, *Folia Hæmatologica*, vii. 1909, 1.

the omentum of a live guinea-pig are either deep or shallow cups and never biconcave. The same is said to be true of human blood examined on a warm stage. So far as our observations go we are unable to accept Weidenreich's view in its entirety. There is no doubt that in practically all blood preparations a certain number of the corpuscles appear to have the bell shape indicated by Weidenreich. Whether these cells are normal or distorted we are unable to say, but their proportion does not increase to the extent we would expect if Weidenreich's view were correct, when special precautions regarding osmosis and temperature are taken.

Effects of Osmosis.—The red corpuscles are extremely susceptible to changes in the salt content of the plasma. Concentration of the plasma from the addition of salts or the evaporation of fluid leads to shrivelling of the corpuscles. The outline becomes jagged and irregular, and such corpuscles are said to be crenated. This appearance is very commonly seen near the edge of blood preparations examined in the fresh state.

Dilution of the plasma causes the corpuscles to swell up and become rounded, and if the dilution be carried too far the corpuscle ruptures and the hæmoglobin passes into solution. The blood is then said to be "laked."

Heat.—If a drop of blood be heated the red corpuscles are broken up as if by explosion. Globules of hæmoglobin separate out, and these are often connected with the corpuscles by long narrow processes.

Pathological Alterations in Shape.—Apart from mere mechanical distortion such as indentation, variation in the shape of the red corpuscles is only seen in anæmic conditions. In anæmia many of the corpuscles may be oval, sausage-shaped, pear-shaped, tailed, or quite irregular in shape. This condition is termed *poikilocytosis.* The amount of poikilocytosis is usually proportional to the degree of anæmia, but it should be kept in mind that in pernicious anæmia poikilocytosis is generally apparently much more marked than in other anæmias of a similar degree, because of the combination with anisocytosis. Occasional cases are met with in which there is but little poikilocytosis.

(*d*) **Structure.**—The erythrocytes are soft, friable, and elastic. They are surrounded by a fine elastic membrane, and consist of hæmoglobin in a loose scanty reticulum, which can be demonstrated by vital staining, and which is easily seen in young cells before their hæmoglobin complement is complete. The erythrocytes have a special affinity for acid dyes, and in health stain but feebly with basic stains.

Polychromatophilia.—In certain circumstances the red corpuscles may show an unusual affinity for basic dyes. This is known as

polychromatophilia or *polychromasia.* At least four different appearances may be distinguished.

1. *Diffuse Polychromasia.*—Two degrees of this condition may be recognised—(*a*) The red corpuscles may show a purple colour when stained with eosine-methylene blue mixtures; with Ehrlich's stain they appear brown. This condition is readily seen in fœtal blood, in experimental anæmia, and in the course of recovery or remission in simple and pernicious anæmias. It is specially common in megaloblasts, rather less so in normoblasts (Plate II., *b*). (*b*) When stained with eosine-methylene blue mixtures the corpuscles show a brownish tinge. This is seen in late fœtal blood and in the course of recovery from anæmia (Plate II., *c*).

Both types are to be regarded as regenerative, and probably indicate stages in the formation or ripening of hæmoglobin, the first type representing an early and the second a later stage of the process.

2. *Granular Polychromasia—Punctate Basophilia.*—This condition is best seen with eosine-methylene blue mixtures. Only a small proportion of the cells show it. It is a special feature of the blood in lead poisoning, in which it is more constant than in any other condition. It also occurs in pernicious anæmia, acute lymphatic leukæmia, grave secondary anæmias of any origin, especially those due to hæmorrhage and to septic poisoning. It may occasionally be found in various toxic conditions, especially in chronic intestinal catarrh.

The granules vary greatly in their incidence in the individual cell and in size; they may be scanty or the cell may be stippled all over.

The condition is often seen in normoblasts and megaloblasts. It is found in cells with the nucleus intact and in cells with dividing nuclei. These facts seem to indicate that the granules are plasmatic and not nuclear. The granules do not stain with methyl green, and are therefore not of the nature of chromatin. They have been described as occurring in bone-marrow and in the blood of new-born infants, and these facts have been taken as suggesting that the granules indicate blood regeneration. This view in simple form we are unable to accept. The stippling appears to us to resemble closely those degenerative granules which occur in the red cells after poisoning with phenylhydrazin and which are undoubtedly degenerative. In clinical work we find that granular red cells appear in greater numbers in proportion to the severity of toxic symptoms, and we look upon them as the expression of a degenerative change in the corpuscle. It is probable that the cells showing the granules are young forms, but the stippling is

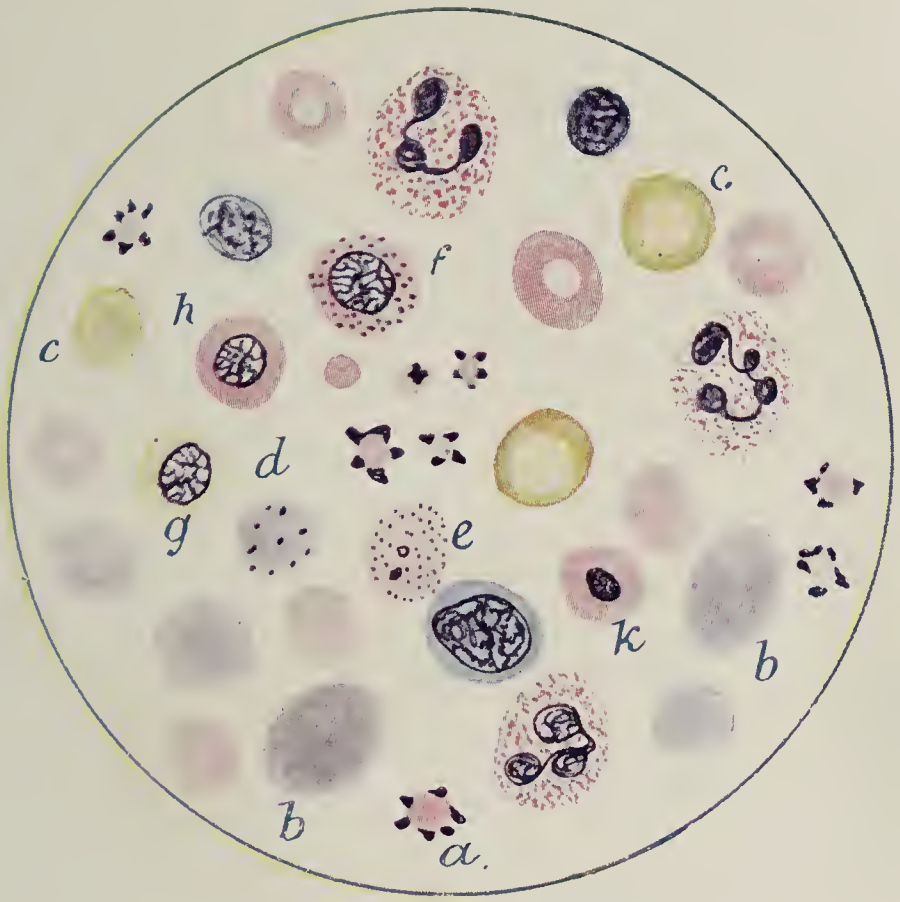


Plate II.—Polychromatophilia.

Blood film from a rabbit three days after injection with phenyl-hydrazin (eosine and methylene blue).

a. Red corpuscle showing degenerated portions.
b. Diffuse polychromasia.
c. Diffuse polychromasia (riper hæmoglobin).
d. Some diffuse polychromasia and granular basophilia (a poisoned young cell).
e. Red corpuscle showing granular basophilia, a "Cabot's ring" and a "Jolly body."
f. Megaloblast showing granular basophilia.
g. Polychromasic megaloblast.
h. Megaloblast.
k. Normoblast.

A. G., *fecit*.

to be regarded as an indication of pathological alteration rather than of mere youth (Plate II., *d*).

3. *Nuclear Particles.*—Red corpuscles showing one or more basophil points are occasionally seen in the blood. They are most frequently seen in conditions in which nucleated cells are present. These particles stain with methyl green and are derived from chromatin. They have been called Howell's bodies and Jolly bodies. The ring-shaped bodies described by Cabot as occurring in the blood in pernicious anæmia are probably of the same nature. These are found either singly or interwoven with others, and measure from 2 to 8 μ in diameter, and are regarded by Cabot as being connected with the former nucleus of the cell (Plate II., *e*).

4. The reticular substance, which can be demonstrated by vital staining, differs from the foregoing types of polychromasia. Indeed punctate basophilia, Jolly bodies, and reticular substance can be demonstrated in the same corpuscle. The reticular substance is found normally in one or two per cent. of the erythrocytes. Cells showing it are more abundant in the blood of the bone-marrow and in the blood of new-born subjects. The reticular cells are increased after hæmorrhage and are present in anæmias. The reticulum is plasmatic in nature, and its presence in many cells probably indicates regeneration of the blood.

Polychromasia, basophil stippling, and reticular substance may all be regarded as different morphological aspects of the same thing—the basophil substance of young erythrocytes, but the stippling is an aspect seen only in pathological conditions.

V. Schilling-Torgau [1] has recently published an important account of his researches on the structure of the erythrocytes. He points out that in the peripheral blood there are corpuscles varying in age from one to twenty days and that their structure may vary accordingly. He has studied the erythrocytes by a variety of methods, including the use of dark-ground illumination, vital staining, different fixatives, and after different degrees of hæmolysis.

He regards the young adult corpuscles as slightly saucer-shaped with a thickened edge. The biconcave disc-forms with a deep hollow on either side are just as much artefacts as the bell-shaped corpuscles described by Weidenreich.

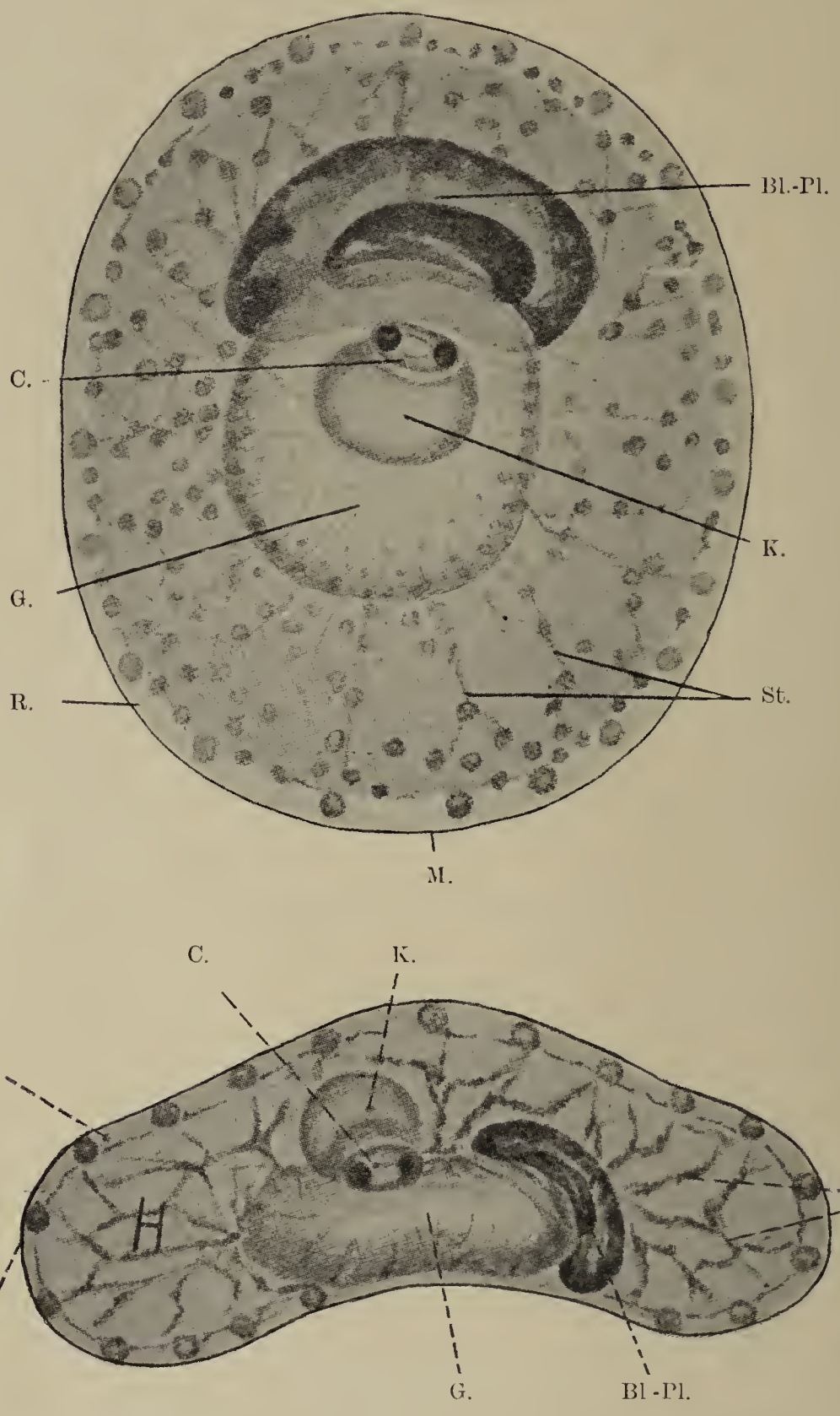
In the typical fully-formed erythrocyte the following parts are recognised.

(*a*) A nucleus or nuclear rest which by a process of physiological metamorphosis has become a blood-plate.

(*b*) Protoplasm consisting of a stroma containing hæmoglobin, an endoplasmic capsule or crust, and an exoplasmic cell membrane.

[1] *Folia Hæmatologica*, xiv. *Archiv*, 1912, p. 95 ; *Centralb. f. Bacteriol.*, lxiii. p. 400.

(c) Archoplasm consisting of a glassy body, a capsule corpuscle, a centriole and scattered granules.



FIGS. 20 AND 21.—COMPOSITE SCHEME OF STRUCTURE OF ERYTHROCYTE (SCHILLING-TORGAU). THE VARIOUS STRUCTURES SHOWN COULD NOT ALL BE DEMONSTRATED AT ONCE IN THE SAME CORPUSCLE OR BY ANY ONE METHOD. FOR ILLUSTRATIONS OF ACTUAL PREPARATIONS THE ORIGINAL PAPERS SHOULD BE CONSULTED. (*Reproduced from the "Folia Hæmatologica" by kind permission of the author.*)

M. Membrane.
R. Space between *M.* and *H.*
H. Hæmoglobin-containing part.
G. Glassy body.
Bl.-Pl. Blood-plate (nucleus).
K. Capsule corpuscle.
C. Centriole.
St. Ground structure with basophilic protoplasmic substance.

The Blood-Plate.—The nucleus of the red cell is like that of other cells only in its early life history. At a later stage the blood-plate represents the

erythroblast nucleus. It arises by a process of physiological modification, possibly mitosis. The plate remains in an eccentric position within the erythrocyte but is easily extruded and destroyed. Plates do not pre-exist free, but they may be extruded and become a third formed element of the blood in the process of making preparations. An abrupt change in structure similar to that from nucleus to plate occurs in the derivation of spermatozoa from spermatids.

It is well known that the erythroblast nucleus is easily extruded, but this only occurs in extreme pathological conditions and in the embryo. It is always rare, and after sufficiently rapid fixation is hardly ever seen.

Any evidence of intracellular solution of the nucleus is to be regarded as due to bad staining.

The alleged disappearance of the nucleus by breaking down (karyorrhexis) is either a pathological process or is quite undemonstrable.

The nucleus disappears without any visible sign in multitudes of young erythrocytes.

"Nuclear rests" such as Howell-Jolly bodies are the result of pathological karyolysis. The blue spherules which may be seen single or double in severe anæmia are in part aggregations of the basophil protoplasmic substance, and their partial origin from nucleoli is not impossible.

Stroma.—There is a protoplasmic stroma, probably somewhat radially arranged and seldom visible.

It lies like a cap round the archoplasm, with its chief mass towards the convexity of the cell. This stroma contains hæmoglobin. In young cells this stroma constitutes the network seen in vital staining, the basic substance which shows as polychromasia, and it may appear as basophilic stippling in pathological conditions. In riper cells it forms the Schuffner's dots which are seen in malaria. The hæmoglobin-containing portion is separated off in a cap or ring-like periphery in young and anæmic cells, so that there is an achromatic central part. In ripe cells a homogeneous saturation of all parts with hæmoglobin is perhaps possible.

The Endoplasmic Capsule.—The protoplasmic substance is thickened at the periphery into a surrounding crust, while the inner portion is more fluid. This crust constitutes the cholesterin-lecithin membrane of Weidenreich.

The Cell Membrane.—The erythrocyte possesses a delicate outer membrane of exoplasm.

"Shadow corpuscles" are essentially hæmolysed stromata separated in layers and are not exclusively exoplasmic vesicles or membranes.

The Glassy Body.—Artificial and pathological alterations of the erythrocytes reveal a sharply circumscribed achromatic (hæmoglobin-free) substance.

Its appearance, isolation, and position in the erythrocyte mark it off as a special structure—the glassy body. This is to be regarded as "rest" material corresponding to the large clear area which is seen round the nucleus in leucocytes and connective-tissue cells, and which provides the achromatic spindle in mitosis. It corresponds in extent to the central clear area seen in erythrocytes prepared in the ordinary way. The glassy body is essentially different from the nucleus and its rests and from "nucleoids."

It may be demonstrated by vital staining, by the dark-ground illumina-

tion combined with vital staining, by rapid fixation of corpuscles by allowing blood to flow into perchloride of mercury or osmic acid, but best of all by a special technique following fixation by Dominici's iodine and perchloride mixture.

A definite grade of fixation is necessary to make the glassy body visible. Too complete fixing makes the bodies just as invisible as they become when ordinary methods are employed. They appear in such circumstances as the clear central portions.

The glassy body can be thrown out of the cell without noteworthy change in the hæmoglobin-containing portion.

This leads to the question whether the glassy bodies are still present in the ordinary erythrocytes of films, and whether they cause the bell shape of the erythrocyte. It is possible in thick films which have been de-hæmoglobinised by Manson's method to demonstrate circular and oval bodies in the hæmolysed corpuscles independent of the central clear area. The form of the erythrocyte has nothing to do with the glassy body. In ordinary circumstances the glassy body is too closely bound up with the structure of the erythrocyte to be noticed independently of it, and it lies quite in the centre of the saucer- or bell-shaped corpuscle.

Half-Moon and Sickle Corpuscles.—These bodies are usually seen as pale, greatly enlarged erythrocytes (15-50 μ) which apparently because of an eccentric vacuole have a sharp sickle-form. They are due to a swelling of the glassy body so that the endoplasmic capsule of the de-hæmoglobinised corpuscle is compressed to one side. They are only produced during the process of observation, but anæmia makes the conditions for their production easy in certain erythrocytes.

They are not specific for anæmia, but a special variety is specific for malaria. The stroma may be pushed to one side or spread out like a ring round the erythrocyte and appear as Schuffner's dots.

Capsule Corpuscle.—This is a body so called because of its resemblance in preparations made by vital staining to the cap of a champagne bottle. It lies eccentrically in the neighbourhood of the clear area. These capsules are identical with Arnold's nucleoids, Schmauch's bodies, Heinz's corpuscles, hæmoglobinogenous bodies, pseudo-nuclei, pseudo-parasites, etc. They apparently arise within the perinuclear area in young cells and remain within the cell after the extrusion of the nucleus. They are to be distinguished from nuclear rests (Jolly bodies, etc.).

Centriole.—This consists of a group of two or more sharply-defined bodies which lie in a soft connecting substance which may show a vacuole. This central group lies in close relationship to the capsule body, but it may become displaced. Both capsule and centriole are surrounded by the clear substance of the glassy body.

Scattered Granules.—There are granular bodies (Meves' plastokonten, etc.) which may sometimes be seen in the region of the archoplasm or occasionally scattered throughout the cell. The nature of these is not yet understood.

(*e*) **Rouleau Formation.**[1]—When blood is shed the red cells run

[1] Literature. See Wiltshire, *Journ. of Path. and Bact.*, xvii. 1913, p. 282.

together to form long rows, each cell fitting into the concavity of its neighbour.

In many anæmic conditions rouleaux formation is deficient. This is probably due to the accompanying poikilocytosis. In making films the spreading should be completed before rouleaux formation has begun.

(*f*) **Numbers.**—In healthy males the average number of erythrocytes is 5,000,000 per c.mm., in females 4,500,000 per c.mm. Counts of over 6,000,000 in healthy persons have been reported, but these are rare, and most counts above 5,000,000, when not due to some obvious cause, are generally to be accounted for by some slight congestion or other circulatory disturbance, it may be of a trifling nature.

Physiological Variations in the Number of the Erythrocytes

1. *Increase—Polycythæmia.*—(a) *Infancy.*—The number of red cells is above the average in the new-born. This is probably due to the rapid loss of fluid by the pulmonary and skin surfaces after birth.

The maximum counts are obtained on the second or third day, and about the end of a week the count is like the adult average.

(b) *Race.*—Race has little influence. M'Cay[1] found a slight excess in Bengalis over the counts in a number of Europeans resident in India.

(c) *Vasomotor Influences.*—High counts are usually obtained after the application of cold, etc., due either to a diminished dilution of the blood by plasma from the subcutaneous tissue, or to a degree of localised stasis in the circulation. Blood drawn from a cold finger contains a larger number of red corpuscles than that from the same finger after it has been warmed. We have found that the red counts in an open-air sanatorium tend to be above the average, and especially so in winter.

(d) *Altitudes.*—A series of records by different observers shows that a definite increase occurs in persons living at high altitudes, and that the increase is proportional to the height. Thus Viault gives the number for the Cordilleras as 8,000,000 per c.mm. The increase soon disappears when inhabitants of high altitudes migrate to lower regions.

The explanation of the increased number of corpuscles is not generally agreed upon. It has been held to be merely an apparent augmentation due to more rapid evaporation of sweat. In view of the fact, however, that the corpuscles are smaller than normal, the

[1] M'Cay, *Indian Med. Gaz.*, October 1907.

probability is that the increased number is simply a means of presenting a larger surface of hæmoglobin to an atmosphere with diminished pressure of oxygen. There is no corresponding increase in the amount of hæmoglobin, and thus the condition seems to be one of altered activity rather than of increased activity on the part of the bone-marrow.

2. *Decrease — Oligocythæmia.* — Physiological diminution in the number of red cells practically does not occur.

Such conditions as normal menstruation, pregnancy, and lactation hardly affect the red cells.

By keeping animals in an atmosphere of compressed air a diminution of corpuscles has been brought about.[1]

Pathological Variations in the Number of Erythrocytes

1. *Increase.*—(a) *Mechanical.*—An apparent increase may result from concentration of the blood caused by acute diarrhœa, profuse sweating, vomiting, and polyuria.

(b) In congenital heart disease an increase of red cells is common.

(c) In acquired valvular disease high counts are occasionally met with (see Chap. XXXV.).

(d) *Toxic Conditions.*—A few excessively high counts have been recorded in diabetes. In coal-gas poisoning and in poisoning by benzine compounds there may be an increase of red cells.

(e) *Splenomegalic Polycythæmia* (*Polycythæmia Myelopathica*) (*Erythræmia*).—A very definite increase in the number of erythrocytes occurs in this condition.

2. *Diminution in the Number of Erythrocytes — Oligocythæmia.*— The causes of oligocythæmia are exceedingly numerous. They include hæmorrhage, blood destruction by parasites or toxins, infective conditions, malnutrition, and disease of the bone-marrow. They will be discussed under these headings.

Nucleated Red Cells, Normoblasts, Megaloblasts, Microblasts

Nucleated red cells do not normally occur in healthy adult circulating blood. While the occasional finding of a nucleated red cell in blood otherwise healthy would indicate an "accident" of no great importance, the presence of nucleated red cells in the blood-stream in even moderate numbers denotes a serious condition.

[1] Doyen et Morel, *Lyon Médical*, 21st July 1902.

The nucleated red cells are found normally in the bone-marrow. There are two chief varieties—normoblasts and megaloblasts—and two types of minor importance—microblasts and intermediate forms.

1. *Normoblasts.*—Normoblasts are of the same size as the ordinary erythrocytes, or may be slightly larger. They are round in shape, and their protoplasm consists of hæmoglobin in a fine reticulum. The nucleus is generally rounded, and measures about 4 μ in diameter.

It consists of a nuclear membrane and thick, densely-packed chromatin, which may appear almost solid, but has an irregularly radial arrangement.

All degrees of karyorrhexis, from mere budding of the nucleus to actual fragmentation, are commonly seen in circulating normoblasts.

Normoblasts can readily be found in the blood of infants for some hours after birth. They rapidly diminish in number, and are not usually found after a week.

2. *Megaloblasts.*—These are cells whose average diameter is much greater than that of the normoblasts. Their diameter may exceed 20 μ. The essential difference, however, is not that of mere size. Thus a nucleated red cell whose diameter exceeded 8 μ might almost certainly be classed as a megaloblast, but a cell smaller than a typical normoblast might yet be a megaloblast. The criterion is nuclear structure. The nucleus is larger, in proportion to the rest of the cell, than that of the normoblast. The nuclear diameter may reach 10 μ. The chromatin strands are much more widely separated, hence the nucleus never appears so deeply stained as that of the normoblast, unless it is degenerated and pyknotic. Many of the chromatin particles show metachromatic staining though true nucleoli have not been demonstrated.

The cytoplasm does not differ from that of the normoblasts. Polychromasia and granular degeneration are more common in nucleated than in non-nucleated red cells, and more common in megaloblasts than in normoblasts.

3. *Microblasts.*—These are nucleated red cells smaller than normoblasts. They are cells which have either been abnormally small from the first or are megaloblasts or normoblasts which have lost part of their cytoplasm. The nucleus may be of either normoblast or megaloblast type.

4. *Intermediate Cells.*—In some nucleated red cells the nuclear structure is not so dense as that of the normoblast or so open as that of the megaloblast. They may be classed with the type of cell they most closely resemble.

The Significance of Nucleated Red Cells in the Circulation.—The megaloblast is ontogenetically an older cell than the normoblast. It is the nucleated red cell of the fœtus. It persists in the bone-marrow, but ceases directly to supply erythrocytes (or rather megalocytes) to the circulation. It gives rise to normoblasts, which become overwhelmingly more numerous in the post-natal marrow and supply the blood with erythrocytes (see HÆMATOGENESIS, Chap. XIII.).

Any ordinary demand for an extra supply of blood-cells is met by increased normoblastic proliferation. This proliferation causes a disturbance of the bone-marrow circulation, so that a varying number of normoblasts may appear in the peripheral blood.

On the other hand, any toxin or hæmolytic agent which not merely affects or is fixed by the circulating blood-cells, but attacks the bone-marrow, leads to a proliferation of megaloblasts, consequently megaloblasts and their non-nucleated descendants, megalocytes, as well as normoblasts and normocytes, may appear in the blood. Megaloblasts, indeed, may outnumber normoblasts in the circulating blood. A megaloblastic anæmia is thus a much more serious condition than a normoblastic anæmia. In megaloblastic anæmia we may consider that not merely the blood but the marrow is affected, and owing to the greater average size of the megaloblasts their appearance in the circulation indicates a correspondingly greater disturbance of the bone-marrow reticulum.

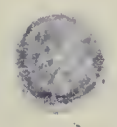
Conditions causing the Appearance of Normoblasts in the Circulation.—Hæmorrhage; secondary anæmia; chlorosis (rarely); pernicious anæmia; leukæmia.

Conditions causing the Appearance of Megaloblasts in Addition to Normoblasts in the Circulation.—Pernicious anæmia; bothriocephalus anæmia; leukæmia; anæmias of childhood; experimental hæmolytic agents—phenyl-hydrazin, toluylen-diamine, etc.


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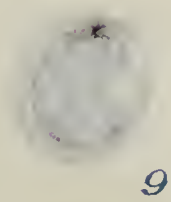

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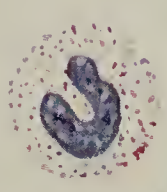

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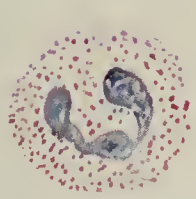

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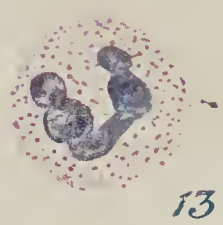

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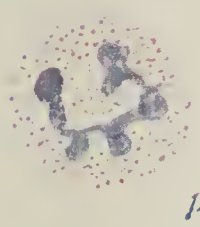

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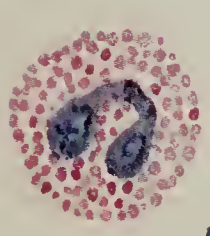

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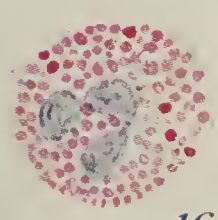

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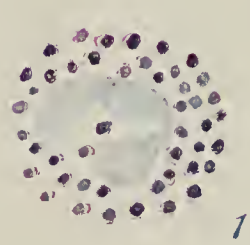

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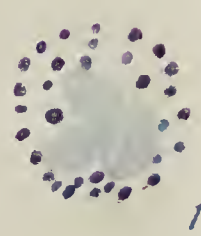

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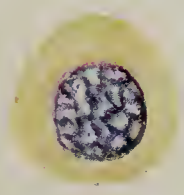

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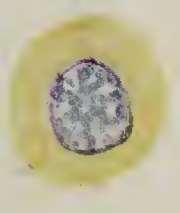

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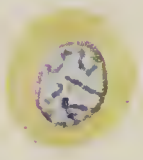

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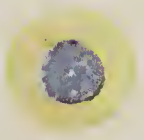

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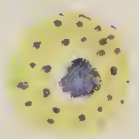

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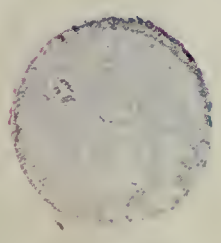

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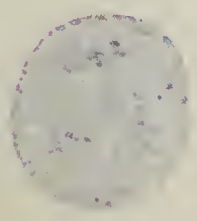

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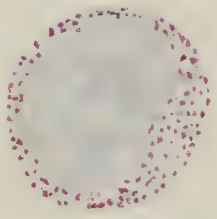

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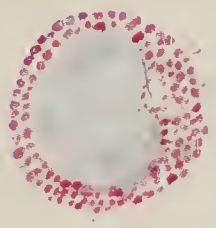

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PLATE III.—TYPES OF BLOOD-CELLS (Jenner's Stain).

1, 2. Red corpuscles.
3, 4. Small lymphocytes.
5, 6. Large lymphocytes.
7, 8. Large mononuclear leucocytes.
9, 10. Transitional leucocytes.
11-14. Polymorphonuclear neutrophil cells.
15, 16. Eosinophil leucocytes.
17, 18. Basophil leucocytes.
19-21. Megaloblasts.
22. Normoblast.
23. Normoblast with punctate basophilia.
24. Myeloblast.
25. Promyelocyte.
26. Neutrophil myelocyte.
27. Eosinophil myelocyte.

A. G., *fecit.*

CHAPTER VII

THE LEUCOCYTES

SEEN in fresh blood, the leucocytes are colourless, highly refractile cells presenting differences in size, in the shape of their nuclei, and in the characters of their protoplasm.

Numbers.—The average number of leucocytes in health is about 7000 per c.mm. The physiological variations may be stated as between 5500 and 9000 per c.mm. The proportion of white to red cells is about 1 to 700.

Classification.—The finer structure of the leucocytes and their different characters can only be made out in stained films. They are classified according to their size, the shape of the nucleus, the presence or absence of granules in their protoplasm, and the staining reactions of those granules. All varieties have a well-developed double centrosome and well-marked nucleoli.

The following are found in the circulating blood:—

1. *Polymorphonuclear Neutrophil Leucocytes.*—These cells vary considerably in size; their average diameter is about 11 μ. The nucleus is lobulated, the different parts being united by strands of chromatin. The number of lobules, their size, and their arrangement vary very greatly. The protoplasm consists of a groundwork and numerous granules. The groundwork has a very slight affinity for stains, but will fix a certain amount of acid dye. The granules are best demonstrated after fixing and staining. They can be stained with difficulty by the use of acid dyes only, but stain best when both an acid and a basic dye are used either in mixture or sequence. Perhaps the best dyes for the purpose are Jenner's and Ehrlich's triple stain. The former method and iron-hæmatoxylin show that the granules are situated on the nodal points of the reticulum (Plate III., 11-14).

2. *Eosinophil Leucocytes.*—The eosinophils are readily recognised even in unstained specimens by the large size and high refractile index of the granules in their protoplasm, but they cannot be distinguished from the next group until their staining reactions have been ascertained. The nucleus has the same general characters as that of the polymorpho-

nuclear neutrophil but is not so convoluted as the former frequently is, and trilobed and spectacle-shaped forms are particularly common. The different parts seem more vesicular and to possess less chromatin than the neutrophils. The protoplasm is packed with large rounded granules which stain deeply with acid dyes. When basic dyes are used the granules stand out clear and unstained (Plate III., 15, 16).

The eosinophils present such a striking picture that there should never be any doubt about their identity. In certain septic and parasitic conditions neutrophil granules stain with special brilliancy. This need not lead to confusion between cells with neutrophil and eosinophil granulation. If there be reasonable room for doubt about the nature of a granular cell it is safe to conclude that it is not an eosinophil.

3. *Basophil Leucocytes — Mast-Cells.* — Basophil leucocytes closely resemble the eosinophils in their general characters. The nucleus is poorer in chromatin and the trilobular is the commonest form. The protoplasm contains a variable number of granules which stain with basic dyes only. They are loosely arranged, and often vary greatly in size in the same cell. They have a special affinity for methylene azur, so that with methylene blue mixtures, especially in alkaline solution, they stain metachromatically with a red-purple tint. In certain cases of myelocythæmia in which eosinophils and basophils are abundant very striking microscopic pictures may be obtained with such a stain as Leishman's, the eosinophils appearing scarlet, the basophils a bright crimson. Basophil granules are not stained with Ehrlich's triple stain or with eosine and hæmatein (Plate III., 17, 18).

4. *Small Lymphocytes.*—These cells are rather smaller than the erythrocytes. The nucleus is round or slightly indented. It stains deeply with basic dyes, and contains irregularly distributed masses of chromatin of varying size. The protoplasm is relatively scanty and often appears as a mere rim round the nucleus. It stains with all dyes—acid, basic, or neutral—but has a special affinity for basic dyes, and particularly for methylene blue. With the latter dye the protoplasm stains darker than the nucleus, and appears to consist of a light blue ground substance in which is embedded a reticulum, the nodal points of which are very fine basophil granules. These granules are considerably smaller than those of the first three varieties.

Larger azurophil granules can be demonstrated in varying numbers in a large proportion of the small lymphocytes. These granules, as well as those of the granular series proper, are probably also situated on nodal points of the reticulum, but it is a little difficult to determine this point, as stains which demonstrate the azur granules do not give satisfactory

pictures of the reticulum. The longer a specimen is stained with Leishman's dye the greater is the number of azurophil granules shown (Plate III., 3, 4).

5. *Large Lymphocytes.*—Large lymphocytes have the same general characters as the small lymphocytes. There are transitions between them, and it is frequently a matter of difficulty to classify some of the intermediate sizes. The large lymphocytes may attain a diametric measurement of 20 μ. The nucleus is generally central, rounded or indented, and contains a less proportion of chromatin than that of the small lymphocytes. The protoplasm is relatively more abundant than in the case of the small lymphocytes, and does not stain so deeply. In addition to the small basophil granules there are frequently azurophil granules in the protoplasm (Plate III., 5, 6).

Large Mononuclear Leucocytes—Transitional Leucocytes.—These are varieties of leucocytes which are frequently classified separately, but which seem to be merely special types of the large lymphocyte. The large mononuclear leucocytes, large hyaline leucocytes or splenocytes, comprise the largest individual cells of the lymphocyte group. The nucleus is generally eccentric, and is small compared to the amount of protoplasm. The protoplasm is abundant, shows a fairly wide separation of the meshes of the reticulum, and consequently does not stain deeply. Azurophil granules are present in varying small numbers (Plate III., 7, 8).

The transitional leucocytes are very similar to the foregoing variety except in the relatively smaller amount of protoplasm and in the shape of the nucleus. The nucleus is considerably indented, and may be horse-shoe-shaped or twisted (Plate III., 9, 10).

The name "transitional" is an unfortunate one. It has no merit as a descriptive term, and is misleading in so far as it suggests that the cell is an intermediate or transitional type. The relationship between the mononuclear cells is discussed in Chap. XIII.

Leucocytes not found in Normal Circulating Blood

1. *Myelocytes.*—Myelocytes are found in large numbers in the bone-marrow, and in pathological conditions may make their appearance in the blood-stream. They are the immediate ancestors or immature forms of the granular leucocytes of the circulation. There are three varieties—

(a) *Neutrophil Myelocytes.*—These show variations in size like the corresponding polymorphonuclear neutrophils, but within wider limits. The protoplasm has a similar slight affinity for acid dyes, but contains

numerous neutrophil granules, which do not stain so well as the polymorph granules. The nucleus is relatively large, and is either round or indented. It does not stain deeply (Plate III., 26).

(b) *Eosinophil Myelocytes.*—These cells have the same relationship to the eosinophil leucocytes as the neutrophil myelocytes have to neutrophil polymorphs (Plate III., 27).

(c) *Basophil Myelocytes.*—Basophil myelocytes are the precursors of the basophil leucocytes. In this form the nucleus is frequently very small. The protoplasmic granules are much more tightly packed than in the basophil polymorphs.

Transitions are found between the myelocyte and the polymorphic in all three types. The nucleus becomes more and more indented, then becomes horseshoe-shaped. Fresh constructions form, and the lobulated condition is finally attained.

2. *Primitive Forms.*—(*a*) In conditions where myelocytes are numerous in the circulating blood a certain number of cells are found which present the general characters of myelocytes but with basophil protoplasm in which scanty neutrophil granules are embedded. Those are known as *pro-myelocytes* (Plate III., 25).

(*b*) Under certain circumstances large mononuclear basophil cells which differ in some respects from ordinary large lymphocytes may occur in the circulation. These cells were described by Naegeli as *myeloblasts.* The protoplasm is intensely basophil, and usually more abundant than in typical large lymphocytes. The nucleus has its chromatin arranged in a fine regular network, and possesses three or four nucleoli, while the typical large lymphocyte has its chromatin arranged in coarse irregular bands and has never more than two nucleoli (Plate III., 24).

(*c*) It may be that in certain cases a cell of an even more primitive type—the undifferentiated primitive leucocyte—may be present.

Plasma Cells.[1]—These cells exist in small numbers in the connective tissues and in the bone-marrow, spleen, and lymph glands. They accumulate in great numbers in the granulomata, especially in syphilitic lesions. They are cells of lymphocyte type which have undergone modification in their sojourn through many generations in an extra-vascular locus.

The cells are often triangular in outline and the nucleus is often tucked away at one corner, so that the cytoplasm is conspicuous. The protoplasm is intensely basophil and granular in character. They are

[1] For discussion and references, see Downey, *Folia Hæmatologica*, xi. i. 275.

best demonstrated by means of Pappenheim's stain after fixation in corrosive sublimate. One per cent. solutions of resorcin, pyronin, and methyl green are mixed just before use in the proportions of pyronin 5 parts, resorcin 10 parts, and methyl green 15 parts. The staining should be controlled by observation under the low power, and slight variations in temperature seem to affect the result. In successful preparations the cytoplasm shows a bright pyronin red, the nucleus a slate green with bright nucleoli. Beside the nucleus is a conspicuous centrosome.

Plasma cells occur in the circulation in some cases of infantile anæmia with jaundice, multiple myeloma, and leucocythæmia.

Pappenheim identifies plasma cells in the blood with the peculiar basophil cells described by Türk as "stimulation forms" (Reizungsformen).

Leucocyte Granules.—Fine granules can be brought out in some of the leucocytes by staining with fuchsin. These are known as Schridde's granules. At one time they were thought to exist only in lymphocytes, but there is no doubt that they also exist in the myeloblasts. Azurophil granules exist in the myeloblasts as well as in the differentiated lymphocytes. They do not ripen to become neutrophil granules but disappear, while the neutrophil granules arise in the protoplasm independently. In young eosinophils some of the granules may stain blue with eosine-methylene blue dyes. These may be looked upon as young or unripe eosinophil granules, but it should be noted that they are basophil, not azurophil.

Differential Counting of Leucocytes.—It is frequently a matter of great diagnostic importance to make a differential count. The principle is easy, the practice laborious. The requisites are an evenly spread and stained blood film, a microscope with an oil-immersion lens, and a paper and pencil. The use of a mechanical stage greatly facilitates the count and increases its accuracy, and Ehrlich's square eye-piece, the aperture of which can be altered, is sometimes an advantage.

A series of columns is headed with the names of all the varieties of leucocytes likely to be met with, and it is convenient to reserve two columns to record the incidence of megaloblasts and normoblasts.

Beginning at (say) the top left-hand corner of the film as it appears under the microscope, one examines the whole top edge of the film passing from left to right. The field immediately below is then brought into view, and the corresponding breadth of film is examined passing from left to right.

Each and every leucocyte (or nucleated red cell) that is seen is noted in the appropriate column. When the total number counted has reached 300 the sum of each variety is divided by 3, and this represents the percentage.

It is often stated that at least 500 or even 1000 leucocytes should be counted in order to give satisfactory percentages. While granting that in theory the greater number counted should lead to greater accuracy, we think it rarely necessary to count more than 300. We have repeatedly been struck by the close agreement of differential counts made in large classes by comparative novices when small total numbers had been counted.

Normal Proportions of Leucocytes.—The proportions of leucocytes which are found in healthy blood vary somewhat. The following limits are physiological :—

Polymorphonuclear leucocytes .	60 to 75 per cent.
Small lymphocytes . . .	15 to 30 ,,
Large lymphocytes (transitionals, etc).	3 to 10 ,,
Eosinophil leucocytes . .	0·5 to 4 ,,
Basophil leucocytes . .	0·025 to 1 ,,

A shorter and convenient statement is—

Polymorphs . . .	70 per cent.	average.
Small lymphocytes . . .	20 ,,	
Large lymphocytes . . .	5 ,,	
Eosinophils	4 ,,	maximum.
Basophils	1 ,,	

Functions of Leucocytes.—Studied on the warm stage the leucocytes are found to be capable of amœboid movement though in different degree. The power of amœboid movement may be regarded as proportionate to the degree of complexity of nuclear structure. Thus the most active cells are the polymorphonuclear neutrophils. The other granular polymorphs come next. The cells of the lymphocyte series show amœboid movements to a less extent, and within the series the power of movement varies with the relationship of protoplasm to nucleus. The nucleus may be regarded as a hindrance to amœboid movement. The transitional cells with their horseshoe nucleus are thus more active than the large lymphocytes, and the large lymphocytes with their relatively abundant protoplasm are more active than the small lymphocytes. Even the myelocytes, which appear in the peripheral blood only in pathological conditions, are capable of a slight amount of amœboid movement.

The leucocytes are also capable of ingesting micro-organisms, their

power in this direction depending upon their amœboid activity and amount of protoplasm. Very large numbers of organisms may be taken up by the polymorph neutrophils on account of their activity, and by the large lymphocytes on account of their size.

Protection.—Their capability of amœboid movement and of phagocytosis, and the fact that the number of leucocytes in the circulating blood is increased in the blood in most cases of infectious disease, indicate that they play an important part in the protection of the body against bacterial and toxic diseases. The *phagocytic index*—the average number of micro-organisms taken up by the leucocytes of a person suffering from a bacterial infection as compared with the average number taken up by the leucocytes of a healthy person under similar conditions—is often ascertained as a means of estimating prognosis or the effect of treatment. The neutrophils are found only in warm-blooded animals. Muir has pointed out that this is due to the fact that organisms develop much more rapidly in the tissues of warm-blooded animals than they do in the tissues of cold-blooded animals, and that therefore this special class of cells has been differentiated to defend the body against them, and that the phenomenon of leucocytosis in warm-blooded animals and the exceeding rapidity of its occurrence has to do with their urgent need of protection. Neutrophil cells are not found in the tissues under normal conditions. They appear there only in response to chemiotactic stimuli, and either perish there or return to the blood when the need for them is past.

The eosinophils seem to have a special relation to the toxins of parasites such as filaria, and possibly also to metabolic poisons such as those concerned in the production of asthma and some skin affections.

The lymphocytes also increase in the peripheral blood in response to invasion by a very limited number of special toxins, such as those of whooping-cough and syphilis. The collections of lymphocytes round the respiratory and alimentary tracts may have to do with the fact that these situations are inhabited normally by attenuated and non-virulent organisms, and that possibly the lymphocytes are adapted and sufficient to keep them in check, and their relatively small percentage in the blood is due to the fact that they multiply so easily in connective tissue that the blood protection can easily be reinforced from that source.

It has been suggested that neutrophils break down to form antitoxins, but of this there is no definite proof.

Absorption and Assimilation of Food.—An increase in the number of leucocytes in the circulating blood takes place during digestion, and

it has been suggested that they play a part in the absorption, transport, and assimilation of protein, fat, carbohydrate, and iron.

Glycogen is easily demonstrated in many of the neutrophils in certain inflammatory conditions, but its significance is not definitely known. It is probably not a degenerative change, and appears more likely to be associated with protection. The glycogen seems to be taken up in the blood and carried to the point which is threatened by organisms, and possibly may there serve to nourish fibroblasts and other young cells.

It has been suggested that the leucocytes play a part in maintaining the constancy of the protein content of the blood plasma. In this connection they might be regarded as secreting glands.

Ferments.—The leucocytes give rise to proteolytic and diastatic ferments, to oxydase, to pro-thrombin and thrombokinase.

The proteolytic ferment is not present in the small lymphocytes.

The proteolytic ferment of the neutrophils is capable of acting in neutral, alkaline, or acid media. The cells in myelocythæmia act best in alkaline media.[1]

The oxydase and blood-clotting agents are discussed elsewhere.

[1] See Longcope and Donhauser, *Journ. of Exper. Med.*, x. 1908, 618.

CHAPTER VIII

VARIATIONS IN THE NUMBER AND PROPORTIONS OF LEUCOCYTES

Diminution of Leucocytes, Leucopenia

I. Physiological.—Diminution in the number of leucocytes only occurs to a very slight extent in physiological conditions. In certain individuals the leucocyte count is always low. The prolonged application of cold or the effect of baths, either hot or cold, may diminish their number.

II. Pathological.—1. In starvation and malnutrition of non-toxic origin the numbers fall.

2. In a few of the acute infections there may be considerable leucopenia. This is notable in typhoid fever. In measles, Malta fever, influenza, and tuberculosis it is usual but not so constant. Injections of serum may cause leucopenia.

3. In infections by animal parasites, malaria, kala-azar, and trypanosomiasis there is usually leucopenia.

4. In some of the blood diseases low counts are found. In pernicious anæmia the number per cubic millimetre rarely exceeds 5000. In splenic anæmia the numbers are still smaller. Rarely in leucocythæmia during a remission or in the course of a complication such as pneumonia the leucocyte count may reach a very low figure.

5. In severe toxæmias when reaction is overwhelmed there may be leucopenia.

6. A transient leucopenia often occurs in traumatic conditions and shock.

In the above conditions the diminution mainly affects the polymorphonuclear cells. Diminution of eosinophils occurs in most fevers, in malignant disease with some notable exceptions, and after hæmorrhage.

Increase of Leucocytes, Leucocytosis

I. Physiological.—High leucocyte counts are physiological under certain circumstances.

1. *Infancy.*—The average leucocyte count in infants during the first four days is about 18,000. The number soon falls, and by the tenth day is about 14,000, by the twelfth month 10,000. The percentage of polymorphs during the first four days is about 66. The polymorph percentage then falls, being about 55 by the tenth day, and as low as 30 about the end of the first year. Between the ages of 1 and 12 years the polymorph percentage is about 50; after 12 it soon approximates to the adult figure. The number of lymphocytes varies correspondingly, the number of eosinophils remaining fairly constant and similar to the adult proportions.

2. *Pregnancy.*—In many instances pregnancy is associated with an increase in the number of white cells.

3. *Digestion.*—An hour after taking food the number of leucocytes begins to rise, reaches its maximum in about four hours, and has fallen to the normal in about six hours.[1] The degree of leucocytosis is greater if food has been previously withheld for at least twelve hours. In ordinary circumstances digestion leucocytosis is but slight (an increase of 1000-1500 per c.mm.), as food is taken at intervals much shorter than the time occupied by the rise and fall which take place after a single meal. In other words, digestion leucocytosis in varying intensity is usually a chronic condition in well-nourished people.

The cells which participate most constantly are the lymphocytes, but the polymorphs may increase to a much greater degree. Eosinophils show very little change, but are usually slightly increased. The source of the leucocytes constituting digestion leucocytosis is the bone-marrow.[2] Protein food causes a greater leucocytosis than fat or carbohydrate.

Young subjects have a greater leucocyte increase after food than adults. It has been found that digestion leucocytosis does not occur in cases of gastric cancer, and in some other conditions such as gastric inertia. During pathological leucocytosis digestion may cause a diminution in the numbers in the peripheral blood.

4. *Leucocytosis of the Moribund—Terminal Leucocytosis.*—A considerable rise in the leucocyte count may occur shortly before death. This does not occur when death occurs suddenly, but when the moribund condition is prolonged the rise in numbers may be considerable, and is probably due to terminal infections. As a rule the increase affects the polymorphonuclear cells. In pathological conditions there may be

[1] See Goodall, Gulland, and Paton, *Journ. of Physiology*, 1903, 1.
[2] Goodall and Paton, *Journ. of Physiology*, 1905, 20.

an exaggeration of the blood picture of the disease in question. In pernicious anæmia there may be a very striking terminal lymphocytosis, but this is rare.

5. A slight increase in the number of leucocytes, chiefly polymorphonuclears, may occur in a variety of conditions, some of which may be mentioned here. These are profuse perspiration, stasis, and emotional conditions, the latter in so far as they may affect the vasomotor system. The short application of cold or cold baths may cause slight leucocytosis.

Exercise and electric stimulation may be followed by a rise in the leucocyte count, and a slight leucocytosis may be determined by the application of a blister.

II. Pathological.—In the course of many diseases there may be considerable increase in the number of white cells in the blood. In practically all cases the increase is brought about mainly by one variety, so that there is marked alteration in the normal proportions. It is therefore convenient to classify the pathological leucocytoses according to the type of cell chiefly involved.

I. *Neutrophil Leucocytosis.*—In most cases the number of cells per cubic millimetre is not very greatly raised. The lower range, from 10,000 to 12,000, is a much commoner finding than the higher counts of 20,000 to 30,000. Simple leucocytoses of 100,000 have been noted, but are very rare. Bunting[1] records a count of 214,000 with 82·2 per cent. of polymorphs in a case of empyema. The blood picture is commonly not greatly altered, the mere presence of an increased number and consequently an increased percentage of polymorphonuclear neutrophils representing the main change. Though the percentage of lymphocytes is usually low, the actual number in the cubic millimetre may be high (see p. 78). In the majority of cases the proportion of large lymphocytes is considerably increased at the expense of the small lymphocytes. Eosinophils and basophils are often absent or reduced to the minimum, especially in septic cases. When, however, the leucocytosis is very great or of long standing a considerable number of myelocytes and young forms make their appearance. Films not infrequently show the presence of a concurrent secondary anæmia.

Causes.—Stated in brief, a neutrophil leucocytosis occurs in malignant disease, in septic and inflammatory conditions, in most fevers and many toxic conditions, and after hæmorrhage.

[1] *Brit. Med. Journ.*, 18th May 1907.

1. *Malignant Disease.*—Leucocytosis is by no means a constant feature. When present it may be of considerable diagnostic significance. Its absence means nothing (Chap. XXXII.).

2. *Septic and Inflammatory Conditions.*—Leucocytosis is the rule in these conditions. Its degree varies very greatly, and seems to depend upon the nature of the organism, the severity of the infection, and the resistance of the individual.

3. *Fevers and Toxic Conditions.*—As a polymorphonuclear leucocytosis is the rule in fevers, it is unnecessary to give a list of the conditions in which it occurs. It is important to note, however, that there are certain exceptions. These are typhoid, influenza (uncomplicated), measles and rötheln, mumps, malaria, and Malta fever.

Tubercular conditions are not usually associated with a polymorph leucocytosis, but it usually occurs in tuberculous meningitis. Smallpox and whooping-cough are also exceptions, as they give rise to lymphocytosis.

The toxic conditions (not specially associated with inflammation) which may bring about a polymorph leucocytosis are very numerous. Some of these may be grouped as follows:—

(*a*) Rickets and gout, acute yellow atrophy, and cirrhosis of the liver.

(*b*) Poisoning by coal-gas, the salicylates or quinine, and the action of hæmolytic agents such as phenyl-hydrazin.

(*c*) Injection of antitoxic serum, organic extracts, nuclein, cinnamate of soda, etc.

(*d*) Injection of irritants such as turpentine, tallianine, croton oil, and copper sulphate.

(*e*) Ether anæsthesia, and rarely after chloroform anæsthesia.

4. *Post-Hæmorrhagic Leucocytosis.*—Soon after hæmorrhage, sometimes within an hour, there is an increase of polymorphonuclear cells in the blood. After a single hæmorrhage the leucocytosis usually disappears in three or four days.

In 1904 Arneth[1] made a division of the polymorphs into five classes according to the number of segments in the nucleus. In the first class he placed myelocytes and neutrophils with indented or horseshoe-shaped nuclei; in the second class, neutrophils with bilobed nuclei; in the third class, trilobed; fourth class, four-lobed; fifth class, five-lobed, or still further segmented nuclei. Each rounded lobule or loop is counted as a segment. A similar classification has since been applied to the eosinophils.[2]

[1] Arneth, *Die neutrophilen weissen Blutkörperchen bei Infektionskrankheiten*, Jena, G. Fischer, 1904. (See *Folia Hæmatologica*, i. 492 *et seq.*; also vii. 83.)

[2] Arneth, *Deutsche Archiv f. klin. Med.*, xcix.

In normal conditions Arneth states the proportions to be as follows :—

Class	I.	II.	III.	IV.	V.	
Neutrophils .	5	35	41	17	2	per cent.
Eosinophils .	11	69	19	1		,,

In toxic conditions he considers that the older cells are killed off more readily, so that there are fewer cells in classes IV. and V., hence the blood-picture is dislocated to the left.

These views have been subjected to much criticism. There is no general agreement that the cells of classes IV. and V. are necessarily older than those of classes II. and III., and some authors hold that certain of the cells with rounded nuclei in Arneth's class I. are not young cells but degenerated forms. In spite of doubt about the significance of the results there is a considerable consensus of opinion in favour of the practical utility of the method. Many suggestions have been offered with the object of facilitating the procedure and of obtaining a simple expression of the results.

Schilling-Torgau[1] classifies the neutrophils as follows :— Myelocytes, myelocytes with notched nuclei, cells with rod-shaped nuclei, cells with segmented nuclei. This classification is much more easily carried out, and is said to convey the same information as a more extended Arneth count.

Pappenheim holds that it is sufficient to state the number of nuclear segments in 100 leucocytes. Another suggestion is that the sum of the percentages in classes I. and II. and half the percentage of class III. should be stated as the nuclear index.

It has been claimed that in fevers and inflammatory conditions Arneth's method is a guide to diagnosis and prognosis, and that in pre-existing illness it may give the first indication of an inflammatory complication. It has its warmest advocates among those who have utilised it as a guide in the administration of serums and the estimation of prognosis in cases of tuberculosis. There is no doubt that in cases with leucocytosis the presence of a moderately high percentage of neutrophils with rounded, kidney-shaped, or horseshoe-shaped nuclei indicates a severe infection. The observer very soon learns to recognise that an unusual number of these cells is present without making a special differential count of the neutrophils.

II. *Lymphocytosis.*—The term lymphocytosis is applied to two groups of conditions—(1) Where there is no increase in the number of white cells per cubic millimetre, but where there is a high percentage of lymphocytes and a correspondingly low percentage of polymorphs (relative lymphocytosis). (2) Where there is increase in the number of white cells per cubic millimetre as well as a high percentage of lymphocytes (absolute lymphocytosis).

The term "relative lymphocytosis" is conventionally applied to the

[1] Schilling-Torgau, *Folia Hæmatologica*, xii. 1 Teil, 1911, 130 (full references to literature).

condition stated above, but only a consideration of the actual figures will determine whether the description "relative lymphocytosis" or "leucopenia" (diminution of polymorphs) is the more accurate. Unfortunately the term "relative lymphocytosis" is often applied to conditions in which there is a low total white cell count with a high lymphocyte percentage although the actual number of lymphocytes per cubic millimetre is normal. These should be described as "leucopenia."

In order to obtain a clear idea of the real relations between the different varieties, it is often advisable to calculate out the actual numbers of each kind of cell in the cubic millimetre instead of expressing them by percentages. Thus, if we take 7000 as the normal number of leucocytes, and use the short table on page 70 for their proportions, we should get the following numbers :—

Polymorphs	4900	
Small lymphocytes	1400	1750
Large lymphocytes	350	
Eosinophils	280	
Basophils	70	
	7000	

If the total count be 4000, and the proportions be

Polymorphs	49
Lymphocytes	48
Eosinophils	3

the beginner is apt to assume that the lymphocytes are considerably increased. When the sum is worked out, however, and the total numbers are found to be

Polymorphs	1960
Lymphocytes	1920
Eosinophils	120
	4000

it is seen that the lymphocytes are well within the normal limit of variation, and that the real change is a diminution of polymorphs. On the other hand, with a leucocytosis of 20,000, with the very common proportions in such a case, of

Polymorphs	90
Lymphocytes	10

the total numbers would be

Polymorphs	18,000
Lymphocytes	2,000

so that the lymphocytes in spite of their low percentage are about the normal, and the increase is due to the polymorphs.

Although for convenience we continue to use the percentage expression, the necessity for this calculation is always understood.

Relative lymphocytosis occurs in—

(1) Congenital and acquired syphilis in the secondary stage, and in uncomplicated tuberculosis.

(2) Pernicious anæmia, chlorosis, scurvy, hæmophilia. (Leucopenia is more common in the first two of these.)

(3) Some cases of goitre and exophthalmic goitre.

(4) Some cases of malaria, typhoid, measles, and mumps.

(5) Some cases of chronic catarrh of the small intestine.

Absolute lymphocytosis is the chief feature of the blood in—

(1) Lymphatic leukæmia.

It also occurs in—

(2) Some cases of tuberculosis and syphilis.

(3) Whooping-cough.

(4) Smallpox.

(5) It has been induced experimentally by injections of pilocarpin (Waldstein [1]), iodine (Bezancon et Labbé [2]), and lecithin, in rabbits by dead non-toxic animal matter (Holmes [3]), and in frogs by injections of bacterial cultures or their filtrates (Proscher [4]).

III. *Eosinophilia.*—Eosinophilia is said to exist when the number of eosinophil leucocytes in the blood exceeds 4 per cent.

The conditions under which this occurs include—

(*a*) Myelocythæmia.

(*b*) Infection by various animal parasites.

(*c*) Certain infectious diseases.

(*d*) Certain cases of asthma during the paroxysms.

(*e*) Some skin diseases.

(*f*) Certain toxic and experimental conditions.

(a) *Myelocythæmia.*—See Chap. XXI.

(b) *Infection by Various Animal Parasites*—(i.) *Intestinal Parasites.*—Eosinophilia may occur in the course of infection with almost any of the intestinal parasites, but only in the case of a few is it constant and definite. It is probable that the factor determining the eosinophilia is irritation of the intestine (see Chap. XXXIII.).

[1] *Berl. klin. Wochenschr.*, 1895.
[2] *Traité d'Hématol.*, 1904, 627.
[3] *Guy's Hospital Reports*, lix. 155.
[4] *Folia Hæmatologica*, i. 1904, 571.

(ii.) *Other Animal Parasites—Bilharzia Hæmatobia.*—Eosinophilia is the rule. Coles [1] recorded a case showing 20 per cent.

Distomiasis.—Ward [2] records a case of distoma hepaticum infection in a man in whom the percentage of eosinophils reached 41·6.

Filariasis.—As first recorded by Gulland,[3] eosinophilia is the rule. Four to 10 per cent. is common. Remlinger [4] found 70 per cent. in cases with chyluria. A slight neutrophil leucocytosis may also be present.

Dracontiasis.—Balfour [5] found 6 to 36 per cent. of eosinophils in six cases of guinea-worm infection.

(c) Eosinophilia occurs in different stages of such conditions as scarlet fever, pneumonia, etc., and will be discussed in connection with these conditions.

(d) *Asthma.*—An increase of eosinophils in the blood and sputum occurs in many cases of bronchial asthma, especially just before and during the paroxysms. The phenomenon may be absent, so that a negative finding has no diagnostic significance. The presence of eosinophilia assists in distinguishing between true asthma and dyspnœa from other causes.

(e) *Skin Diseases.*—In some diseases of the skin there may be considerable eosinophilia. The conditions in which it is most constant are pemphigus and dermatitis herpetiformis. With much less frequency eosinophilia occurs in other bullous eruptions, urticaria, and eczema.

(f) *Toxic and Experimental Conditions.*—(i.) Eosinophilia has been recorded in osteomalacia, chronic osteomyelitis, rickets, and bone tumours.

(ii.) Phosphorus poisoning has been stated to cause eosinophilia.

(iii.) Eosinophilia has been caused in rabbits by intravenous injections of extracts of tænia saginata in salt solution (Proscher and Pappenheim [6]). The eosinophils are nearly all myelocytes.

IV. *Basophilia.*—Basophilia occurs in the following conditions:—

(*a*) Myelocythæmia (Chap. XXI.).

(*b*) *Staphylococcus Infections.*—Some degree of basophilia may occur in the human subject. It has been produced experimentally in rabbits by injections of staphylococcus toxin.

[1] *Diseases of the Blood*, 1905.
[2] *Brit. Med. Journ.*, i. 1911.
[3] *Brit. Med. Journ.*, 1902.
[4] *Soc. de Biologie*, 1902.
[5] *Lancet*, 1903.
[6] *Folia Hæmatologica*, i. 638. (An account of other experimental leucocytoses is given here.)

(*c*) Injections of pyrodin, hemialbumose, colchicine, and phrynolysin have been found to cause basophilia. The latter brings about an increase of mononuclear basophils (Proscher and Pappenheim). Similar results have followed the injection of milk and cancer extracts.

(*d*) Occasional instances of a minor degree of basophilia are not very rare. At present, however, there are no data which would permit of any grouping of these cases. Dickson [1] found an increase up to 2 per cent. in four cases of acromegaly.

[1] Dickson, *The Bone Marrow*, Longmans.

CHAPTER IX

THE BLOOD-PLATES: HÆMOCONIA

Blood-Plates.—In a drop of fresh blood the blood-plates appear as colourless, refractile, discoid bodies, varying in size from 1 to 3 micromillimetres in diameter.

They show a great tendency to adhere to each other and to any foreign body with which they may come into contact. This leads to considerable difficulty in studying their morphology and in estimating their numbers. In films stained by eosine-methylene blue combinations, such as Jenner's stain, they show an affinity for basic dyes. Their outlines are rather indefinite and irregular, and in the centre they usually exhibit an area of chromatin substance staining more intensely than the periphery. This is regarded by some observers as a nucleus. It is brought out much better by such Romanowsky modifications as Leishman's and Wright's stains, with which the central bodies stain a brilliant red, like the nuclei of leucocytes.

Opinions vary considerably regarding the nature of the blood-plates. The chief views regarding them are as follows :—

1. That they are broken pieces of white cells or their nuclei (Max Schultze, Riess).

2. That they are nuclear remains derived from red corpuscles by extrusion (Engel, Pappenheim, Maximow, Schwalbe, Arnold). That they represent the normoblast nucleus, altered by a process of physiological metamorphosis as described on page 57 (Schilling-Torgau).

3. That they are nucleated cells which constitute a third type of formed element of the blood (Hayem, Bizzozero, Deetjen).

Deetjen[1] studied the blood-plates on glass slides covered with a film of jelly made as follows :—

5 grms. agar are boiled in 500 c.c. distilled water for half an hour.

To each 100 c.c. of filtrate are added—

0·6 grm. sodium chloride.

6·8 c.c. of a 10 per cent. watery solution of metaphosphate of sodium (Merck).

5 c.c. of a 10 per cent. watery solution of potassium bisulphate.

[1] Deetjen, *Archiv f. Path. Anat.*, 1898, 164.

His observations on the warm stage led him to the conclusion that the blood-plates were nucleated cells capable of amœboid movement.

4. That they form an independent but non-nucleated element of the blood.

5. That they are precipitates from the plasma.

The vastly greater number of plates which appears when Deetjen's method is employed suggests the view that a proportion of the plates at least are precipitates.[1]

6. That they are detached portions of the cytoplasm of the giant cells of the spleen and bone marrow (Wright,[2] Bunting,[3] Downey [4]).

In sections stained by his modification of Leishman's method Wright finds that the blood-plates show a light blue hyaline periphery and a central part crowded with red or violet granules. He finds the same differentiation of the giant cell protoplasm, and notes a marked tendency of the giant cells to form pseudopodia. These pseudopodia may project into vessels, and often show constrictions and segmentation into bodies which resemble the blood-plates. He further points out that only in mammals are blood-plates found, and that only in mammals are giant cells found.

He also notes a parallelism between the number of plates and giant cells in various pathological conditions.

Many authorities admit a multiple origin of the blood-plates, and some make a distinction between plates derived from red cells and plates derived from white cells.

There are difficulties in the way of accepting any of the views hitherto propounded, and while we may state that we regard the blood-platelets as derivatives of the white cells, particularly polymorph nuclei, we offer the opinion with no great confidence. We consider that these plates exist in the blood before it is shed.

The so-called blood-plates which increase in the plasma after blood is shed are to be regarded as precipitates.

Number of Blood-Plates.—Very diverse statements are made regarding the number of blood-plates in health. The average may be taken as 300,000 per c.mm.[5]

Variations in Pathological Conditions—Diminution.—1. The blood-

[1] Buckmaster, *Morphology of Normal and Pathological Blood.* London, 1910.

[2] Wright, *Boston Med. and Surg. Journ.*, 1906, 643.

[3] Bunting, *Journ. Exp. Med.*, xi. 451.

[4] Downey, *Folia Hæmotologica*, xv. *Archiv*, 1913, p. 25.

[5] See Pratt, *Journ. Amer. Med. Assoc.*, 1905 ; Tschistowitsch, *Folia Hæmatologica*, 1907, 295 ; and Aynaud, *Thèse de Paris*, 1909, Steinheil, for discussion and references to literature.

plates are diminished in infectious diseases [with the exception of scarlet fever (Tschistowitsch)] during the febrile stage. They are diminished in infection by animal parasites.[1] There is no relationship between the number of blood-plates and leucocytes.

2. The plates are diminished in hæmophilia, purpura, and leucocythæmia.

3. There is a great reduction in the number of blood-plates in pernicious anæmia, but they are often greatly increased in size.

4. They are diminished in cachexia, malnutrition, and in some cases of cancer. In cancer with marked secondary anæmia the plates may be normal or increased.

Increase.—1. There is a marked increase of blood-plates after even slight hæmorrhage.

2. They are increased in most cases of chlorosis.

3. They are increased in most inflammatory and septic conditions.

Hæmoconia.[2]—Hæmoconia consist of small, colourless, highly refractile bodies which are found in normal and pathological blood. They are usually round, but may be rod-shaped or dumb-bell-shaped. They vary in size from 0·5 to 4 μ. They exhibit Brownian movement. They do not stain with ordinary methods, nor with osmic acid or sudan. The nature of these bodies is uncertain. Some of them are doubtless extruded leucocyte granules or pieces of broken cells. Mühlmann considers that they are in part, at least, of a fatty nature, and finds that they are increased in the blood after a meal rich in fat.

[1] Darling, *Trans. Soc. of Trop. Med. and Hygiene*, v. 1911.

[2] Müller, *Centralb. für allg. Path.*, 1896; Stokes and Wegefarth, *Johns Hopkins Hosp. Bulletin*, 1897; Love, *Lancet*, 1904; Mühlmann, *Berl. klin. Wochenschr.*, 1907; Porter, *Brit. Med. Journ.*, 1907.

CHAPTER X

THE BLOOD IN INFANCY, OLD AGE, ETC.

Infancy and Childhood.—*Red Corpuscles.*—At birth the number of red corpuscles is high—on an average about 6 millions per c.mm. This condition is due to the loss of fluid which occurs after birth by evaporation from the skin and respiratory passages, while there is little or no addition of fluid to the body for some days.

Aspiration from the placenta plays a part in determining the number of corpuscles in infantile blood, since they are more numerous when ligature of the cord has been delayed than when it has been tied promptly.

The hæmoglobin shows a correspondingly high percentage, the usual reading being about 120 per cent. This figure may be exceeded, and not infrequently the colour index tends to be high from the fact that the corpuscles, like those of fœtal life, are larger than in adult life. There is slight variation in the size of the red cells, and in some healthy infants there may be a slight degree of polychromasia.

Nucleated red cells (normoblasts) are always present in the circulating blood of infants for some time after birth. They are fairly numerous in the first three or four hours, but after that they rapidly diminish, and are to be found only with great difficulty after seven days.

The polycythæmia soon disappears, and the ordinary numbers are reached by the end of the second week.

The hæmoglobin percentage also falls, but the fall is not arrested when it has reached 100 per cent. The percentage continues to fall gradually throughout infancy, and remains about 80 per cent. till the age of ten years is reached, when it begins to increase again, and a child of twelve should have 100 per cent.

White Cells.—The leucocyte count at birth is high, and frequently numbers 18,000 per c.mm. The count tends to rise a little during the next two days, and may reach 30,000. This is succeeded by a rapid fall, so that at the end of the first week the number may not exceed 10,000.

After the first week the white cells again increase. At eight months the number is about 15,000, and at twelve months 10,000. A gradual fall continues during the next five years. At six the number is about 9000; at nine, 8000; and by twelve the adult figure is reached.

There are corresponding variations in the proportions of the different cells. The variations in the first week are due to a rise and fall in the number of polymorphs. They may reach a maximum of 70 per cent. and fall to 20 per cent. During infancy and early childhood the rule is a high percentage of lymphocytes.

From the tenth day till about the fourth year they are in excess of the polymorphs. About the tenth day they constitute 60 per cent. of the white cells, and they remain in about this proportion till the third or fourth year, when they fall to 50 per cent. A gradual fall continues, so that the adult proportions are reached about twelve years of age.

The other white cells show the same kind of variation that may be noticed in the adult, but there are no variations corresponding to age. If for any reason the development of a child is delayed or its nutrition impaired, the lymphocyte proportion is found to be higher than it should be for that age.

The white cells in infancy and childhood are much more responsive to stimuli than in adult life. During digestion the increase may be very great, and during the first three years of life the number during fasting may be doubled or trebled after a meal.

The leucocytes also respond more readily and more largely to toxic stimuli, and the proportion of lymphocytes always tends to be greater than in corresponding conditions in the adult.

Old Age.—There are no changes of importance.

Menstruation.—Slight variations in the cells of the blood and the amount of hæmoglobin have been recorded. Even the most extensive of the recorded findings are too slight to be of practical importance.[1]

Pregnancy.—There is often a slight decrease of red cells towards the end of pregnancy in primiparæ. This does not occur in multiparæ.

In many instances, especially in primiparæ, there is an increase of white cells. The increase becomes noticeable after the third month,

[1] See Polzl, *Münch. med. Wochenschr.*, 1910, 333.

counts then averaging about 12,000. There is a gradual increase up to the end of pregnancy. The increase is shared in by polymorphs and lymphocytes in pretty much the normal proportions.

During labour the number of leucocytes rises, and may reach 20,000. The count falls after the third stage, and has reached normal by the end of the second week.

Lactation.—The blood is not affected.

CHAPTER XI

THE BLOOD IN CERTAIN ANIMALS

A GREAT many observations on the blood of the various domestic and commonly used laboratory animals are to be found scattered throughout the magazines, but no very exhaustive account has yet been published. The following data are derived from our own observations and from various sources, and enough references are given to put any worker on the track of literature he may wish.

Blood counts in laboratory animals are apt to vary considerably from different causes. The differences are sometimes due to individual peculiarity or to differences in feeding or environment, and it should be remembered that anæmia and parasitic conditions are common and may modify the blood.

Animal.	Observer.	Red Corpuscles per c.mm.	Hæmoglobin as Percentage of Human.	Leucocytes per c.mm.	Polymorphonuclear Leucocytes.	Lymphocytes.	Eosinophils.	Basophils.
Horse .	Burnett.	7,500,000	90	10,000	60	35	4	1
,, .	Sabrazès.	8,068,000	73	6,433	37·5	58	2·5	2·5
,, .	Mezincesci.	...	...	10,000	32-60	34-69	2-6	0·2
Ox . .	Burnett.	6,500,000	60	8,000	30	55	14	1
Sheep .	,,	10,000,000	...	7,500	38	60	1·5	0·2
Goat .	,,	14,000,000	...	12,000	...	...	...	...
Pig . .	,,	7,000,000	...	13,000	39	55	5	1
,, . .	Giltner.	8,450,000	88	19,000	37	56	5·2	1·3
Dog . .	Authors.	5,599,000	90	19,500	63	30	7	...
,, . .	Burnett.	6,500,000	...	10,000	63	25	12	...
Cat . .	Authors.	8,000,000	70	18,000	54	37	9	...
,, . .	Burnett.	8,000,000	...	13,000	55	40	5	...
,, . .	Busch and v. Bergen.	6,609,000	...	13,330	60	39	0·9	...
Rabbit .	Authors.	5,160,000	74	10,500	43	52	2·5	2·5
,, .	Burnett.	5,500,000	74	8,500	47	48	3	2
Guinea-pig	Authors.	5,600,000	100	9,170	37	60	3	...
,,	Burnett.	5,500,000	...	9,000	47	50	2	1
Rat . .	Authors.	8,100,000	110	10,600	28	68	3	1
Mouse .	,,	10,850,000	90	5,000	23	71	5·75	0·25
Llama .	Biffi.	11,546,600	...	10,741	75	22·8	1·5	...
Hedgehog .	Authors.	8,800,000	...	8,500	37	56	6	1
Fowl .	,,	3,200,000	...	19,000	37	56	6	1
,, .	Burnett.	3,000,000	...	25,000	27	65	5	3
Frog .	Authors.	500,000	...	11,000	7	59	27	7
Skate .	Fraser Harris.	350,000	...	27,500	...	...	...	...

In the case of the more common laboratory animals we may state the extremes which we have found in healthy conditions—

Animal.	Red Corpuscles.	Haemoglobin.	White Cells.	Polymorphs.	Lymphocytes.	Eosinophils.	Basophils.
Dog	5,500,000	110	31,200	60	25	14	...
,, ...	4,750,000	75	11,200	78	20	2	...
Cat	8,600,000	80	38,800	74	20	6	...
,, ...	7,280,000	65	15,800	40	56	4	...
Rabbit	5,760,000	90	16,000	50	48	1	1
,, ...	4,560,000	70	7,200	32	62	4	2
Guinea-pig . . .	6,880,000	120	...	21	71	8	...
,, . . .	4,800,000	90	...	52	42	6	...

The number of white cells in guinea-pigs seems to increase with the age of the animal, as the following table indicates :—

I.		II.		III.		IV.	
Weight in grms.	Leucocytes per c.mm.	Weight.	Leucocytes.	Weight.	Leucocytes.	Weight.	Leucocytes.
110	7,400	230	8,400	320	11,200	450	8,800
140	11,600	230	8,000	325	8,200	460	15,400
150	3,000	260	6,400	335	6,600	480	5,800
155	12,400	285	6,600	390	14,000	530	10,400
160	7,800	290	9,000	380	10,200	570	14,800
170	2,400	...	...	395	5,600	670	9,600
170	2,600	...	...	...	...	675	16,400
175	8,800	...	...	...	...	680	20,400
185	2,800	...	...	...	...	790	17,000
Average .	6,537	...	7,680	...	9,300	...	13,177

Horse and Ass.—Red corpuscles measure 5·5 μ. The polymorph nuclei show an unusual degree of lobulation. The neutrophil granules are very fine. The eosinophil granules are spherical or ovoid and are very large.

Ox.—Red corpuscles measure 5·6 μ. General morphology does not differ greatly from that of human blood.

Sheep and Goat.—Red corpuscles measure 5 and 4·1 μ respectively. The neutrophil granules are closer together and are very much smaller

than in human polymorphs. Kurloff's bodies (see *Guinea-pig*) are fairly numerous in the large lymphocytes of the sheep.

Pig.—Red corpuscles 5·6 μ (8·5 μ Giltner; 6·2 μ Gütig). Neutrophil granules are very fine.

Dog.—Diameter of red cells 7 μ. The protoplasm of the polymorphs has a slight neutrophil reaction, and prolonged staining is required to demonstrate distinct granules. The eosinophils have not such a special affinity for eosine as for orange. Mast-cells are very rare.

Cat.—Red corpuscles 6·5 μ. Granules are present in the polymorphs, but they are exceedingly fine and very difficult to demonstrate. Prolonged staining is required (Leishman, half an hour). The protoplasm tends to stain diffusely in the same tint as the granules. The eosinophils have large ovoid granules. Basophils are found in very small numbers.

Rabbit.—The red cells are poor in hæmoglobin and look anæmic. Average diameter 6·5 μ. The polymorphs contain large amphophil granules (pseudo-eosinophils). There are also true eosinophils with more densely packed granules. Mast-cells are relatively abundant. Wild rabbits generally give higher counts, especially of red cells, than do the domestic variety.

Guinea-pig.—Red corpuscles measure 7·5 μ. The polymorphs contain large amphophil (pseudo-eosinophil) granules. The eosinophil granules resemble those of man, but they are divisible into two groups which have somewhat different affinities for dye stuffs. In many of the large lymphocytes there are large vacuoles which may be empty, but which generally contain a homogeneous structure which stains in the tone of the neutrophil granules. These are known as "Kurloff's bodies." They probably consist of a cellular secretion, but have been thought to be parasites. Schilling-Torgau regards them as chlamydozoa. Ross considers them to represent one phase of the life-history of a spirochæte.[1]

Rat.—The diameter of the red cells averages 5·8 μ. The polymorphs contain rather scanty and fairly large granules. Many of both polymorphs and eosinophils have ring-shaped nuclei.

White Mouse.—Red corpuscles measure 5·6 μ. The lymphocytes are mostly large, with relatively large nucleus and faintly basophil protoplasm, which contains a good many azurophil granules. The polymorphs are usually stated to be non-granular, but it is possible with prolonged staining to demonstrate fine and very scanty neutrophil

[1] For references to literature, see *Folia Hæmatologica*, xii. xiii. *Centralbl.*

granules. These cells are very labile. In the eosinophils the granules are often scanty and may be arranged in patches. Ring-shaped nuclei occur, and unless films are carefully spread the polymorphs, whose granules are often unstained, may be mistaken for lymphocytes.

Hedgehog.—Red cells measure about 4·5 μ. The fine basophil granulation of the lymphocytes is very distinct. The polymorphs have distinct granules. There are about 1 per cent. of basophil myelocytes. The granules in some of them are very large.

Fowl.—The great majority of the red cells are oval and nucleated with a long diameter of 11·2 μ. A few, however, are round, and in these the nucleus shows a wider chromatin network. These cells correspond to the large nucleated red cells of mammalian blood, and are probably younger cells than those with oval nuclei. Even earlier forms are found in the circulation. These are oval, nucleated, but non-hæmoglobin-containing corpuscles. They are usually smaller than the ordinary forms. They are the youngest type of cell. Again, a few old cells are to be found whose nuclei have disappeared. The white cells are peculiar. There are lymphocytes and eosinophils resembling those of mammalian blood. There are no ordinary neutrophils. Their place is taken by polymorphonuclear cells, whose protoplasm contains a large number of rod-shaped crystalline bodies with a marked affinity for eosine. Basophils are present in considerable numbers. They are myelocytes with a relatively small pale nucleus and a pale protoplasm, in which the scanty basophil granules varying in size are to be seen. Blood-plates are absent. Small lipoid bodies (hæmoconia) are to be found in small numbers.

Frog.—The red cells have to some extent the same general characters as those of the fowl. The typical cell is flattened, oval, and biconvex, with a thickened equatorial area. There is an oval nucleus. The long diameter measures 22 μ. Young forms are also found. These are small oval cells without hæmoglobin, and round hæmoglobin-containing cells with the megaloblastic type of nucleus. Non-nucleated forms occur with rather greater frequency than in the fowl. The white cells are lymphocytes, polymorphs, often with fragmented nuclei and without granules, eosinophils, and basophil myelocytes.

Literature.

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CHAPTER XII

SOURCES OF THE BLOOD-CELLS. THE BONE-MARROW AND ITS REACTIONS

Sources of the Blood-Cells.—The sources of the blood-cells are the lymphoid tissues throughout the body, and the bone-marrow. The former supply only lymphocytes, and even this function is shared largely by the marrow. The structure of the lymphoid tissues is simple and (so far as their effect on the blood is concerned) the changes which they undergo in disease may be regarded as hyperplasia and atrophy. The marrow, on the other hand, has a more complicated structure, and is subject to diverse and profound alterations.

Structure of Bone-Marrow.—1. *Fœtal Marrow.*—In early fœtal life the bone-marrow consists of the embryonic mucous tissue which when ossification begins invades the cartilage of long bones or the fibrous tissue which precedes the flat bones.

This tissue is invaded by primitive leucocytes and nucleated red cells in the third month of fœtal life. These cells form little islands of leucoblastic or erythroblastic tissue which extend and may meet each other. Very soon fat is deposited in the young fibrous tissue, and this mixture of fat-cells, red cells, and white cells constitutes the red bone-marrow.

2. *Yellow Marrow.*—After fœtal life the amount of bone-marrow is greater than the requirements of blood formation in health. The hæmopoietic function of the marrow in the shafts of the long bones is lost and it becomes yellow marrow. This consists merely of fatty fibrous tissue, but as at any time in disease the yellow marrow may resume its blood-forming functions, it remains of potential hæmopoietic interest.

3. *Red Marrow.*—The red bone-marrow occupies the flat bones and the extremities of the long bones. It is the sole source of the red cells and the main source of the white cells in post-natal life.

The red marrow has a supporting framework of fibrous tissue forming a reticulum and containing a large number of fat-cells.

Wide thin-walled capillaries or sinusoids traverse this reticulum, anastomosing freely with each other and opening directly into the spaces in which the marrow-cells lie.

Some observers have sought to show that the cells forming red cells are intravascular, while the leucocytic areas are extravascular. We cannot find evidence of this on histological grounds.

Between the fat-cells are great numbers of blood-cells. Red and white cells are in about equal proportions and are indiscriminately mixed. Areas consisting exclusively of one variety of cell are very small. A large proportion of the red cells are nucleated (normoblasts) and there are a few megaloblasts. There are also a few erythroblasts without hæmoglobin.

All the varieties of leucocytes met with in the blood are to be found in the bone-marrow. The most abundant, however, is the myelocyte, which does not normally escape into the circulation. The proportion of myelocytes (neutrophil, eosinophil, and basophil) to each other is much the same as that of the polymorphonuclear forms in the blood. More primitive types (pro-myelocytes and undifferentiated lymphocytes) are also present in smaller numbers. Ordinary lymphocytes are found to the extent of about 20 per cent. Polymorphs do not exceed 10 per cent.

A striking cell found in small numbers is the giant cell (megakaryocyte). This cell may measure over 30 μ in diameter. Its protoplasm is acidophil; the nucleus is convoluted and basket-shaped. The latter often appears horseshoe-shaped in section, and consists of several little rounded masses with fine connections.

This cell should not be confused with the multinucleated osteoclast found in connection with developing bone (Plate IV.).

Bone-Marrow Reactions and Degenerations.—The bone-marrow very readily responds to different stimuli. The stimulus may be such that there is special activity on the part of the red cells (erythroblastic reaction) or on the part of the white cells (leucoblastic reaction). Both may be present at the same time. In these processes the marrow becomes more vascular, and the reaction may extend into the yellow marrow in the shafts of the long bones. The hæmopoietic cells increase at the expense of the fat-cells, and if the activity be considerable the spicules of cancellous bone and the walls of compact bone may be partly absorbed to make more room.

Erythroblastic Reaction.—This is of two kinds—normoblastic and megaloblastic.

1. *Normoblastic.*—The marrow becomes more vascular and there

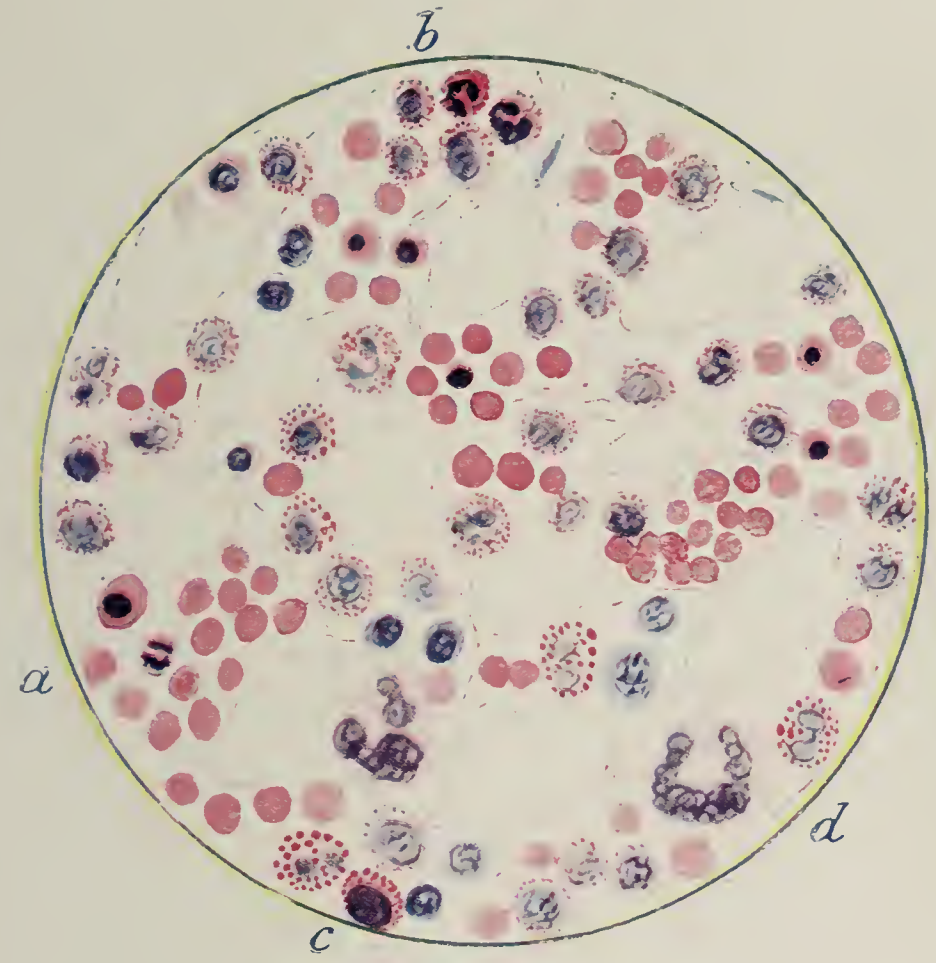


Plate IV.—Normal Red Marrow.

a. A group of red corpuscles and normoblasts, one in mitosis.
b. A group of neutrophil leucocytes, myelocytes and polymorphs.
c. An eosinophil myelocyte and polymorph.
d. A giant cell. Immediately above it are two lymphoctyes and a fat-cell.

A. G., *fecit*.

may be extension of hæmopoietic function into the yellow marrow, which becomes red.

On microscopic examination there is a great increase in the number of erythrocytes and normoblasts, and many of the latter show mitotic figures. In most cases there is concomitant activity on the part of the myelocytes, but where the stimulus is long continued the white cell activity may subside, and in such cases the majority of the white cells are lymphocytes. This state of affairs indicates a certain degree of marrow exhaustion, as might be inferred from the comparative frequency with which it is found in the post-mortem room. Normoblastic bone-marrow reaction is found most typically after hæmorrhage.

2. *Megaloblastic.*—In this condition the marrow is very red and all the yellow marrow in the body may be transformed to active hæmopoietic tissue. The reaction is probably always due to disturbance of the marrow itself and is not a mere response to a demand for an increased output of red corpuscles. The microscope reveals a picture of remarkable activity. Megaloblasts are found in enormous numbers, and a very large proportion of them show mitotic figures.

The reaction is often associated with myelocytic activity, but in perhaps 40 per cent. of cases lymphocytes preponderate among the white cells. Megaloblastic bone-marrow is typically found in pernicious anæmia.

Leucoblastic Reaction.—In response to various stimuli there may be great activity of the white cells. The causes are those which bring about leucocytosis in the peripheral circulation, and the stimulus may specially affect one or more of the different varieties.

The cells most commonly affected are the neutrophil myelocytes. When the reaction is severe a large amount of yellow marrow may be involved, and owing to increased vascularity it becomes red in colour, though not so red as in the erythroblastic reaction.

Myelocytes, and to a certain extent their non-granular precursors, are actively dividing. There is no accumulation of polymorphs in the marrow, since they are hurried into the circulation, in many cases even before they are mature.

Certain toxins bring about special activity on the part of the eosinophils or basophils, either alone or along with neutrophils.

In children and in a few diseases there is special activity on the part of the lymphocytes.

The special marrow conditions associated with leukæmia will be discussed in connection with that disease.

It is to be noted that while special erythroblastic activity is usually associated with leucoblastic activity, the reverse (if we exclude leukæmia) does not occur.

Another point which deserves passing notice is the fact that the peripheral blood does not always reflect the condition of the marrow. Thus we may find an abundant polymorph leucocytosis before death, yet polymorphs may be very scanty in the marrow. The explanation here is probably that suggested above, viz. that the polymorphs are turned out as soon as they are ripe, and there may be a special emigration just before death.

A more puzzling state of affairs is the condition often found in pernicious anæmia in which the marrow of cases showing a marked diminution of polymorphs in the circulation is found to present a picture of remarkable myelocytic activity.

Bone-Marrow Degenerations—Fatty Degeneration.—In this condition there is a diminution in the number of hæmopoietic cells, and only small islands, consisting mainly of lymphocytes, are seen at intervals separated by several fat-cells.

The condition is, of course, not primarily a fatty degeneration, but is a phase of exhaustion of the blood-forming cells. It is brought about (1) by severe toxæmias which overwhelm, rather than stimulate, the marrow; (2) by repeated or continuous hæmorrhage, as in some cases of hæmophilia and purpura; (3) it occurs in aplastic anæmia.

Fibroid Degeneration.—The reticulum is thickened, and there may be increase in the fibrous tissue to such an extent as to diminish the amount of hæmopoietic tissue. The degeneration occurs in old age, in cases of debility, and in syphilis.

Gelatinous Degeneration.—This condition may occur as a primary change in cases of inanition, but much more commonly it represents a phase of marrow exhaustion after severe stimulation. Stockman and Charteris[1] found that it followed great marrow activity in animals after prolonged administration of lead, mercury, and arsenic. It also occurs in toxæmias due to infection or malignant disease. The naked-eye appearance of the marrow varies with the condition preceding it, as it may supervene in a fatty marrow or in a marrow actively leucoblastic or erythroblastic. There is always a somewhat glistening homogeneous appearance, with increased translucency. The microscopic change consists in an absorption of the fat-cells, whose capsules may appear shrivelled. The blood-forming cells also disappear, so that the cells

[1] *Journ. of Path. and Bact.*, ix. 1903.

and fibres of the reticulum become unusually conspicuous, and give a curious fibrillated appearance to some sections. In others, possibly representing an earlier stage before the fat is completely absorbed, the marrow appears unusually homogeneous. The blood-forming cells are found in somewhat widely scattered areas. The kind of cell which preponderates is usually the lymphocyte with the representatives of the cellular activity before the gelatinous change supervened.

CHAPTER XIII

DEVELOPMENT OF THE CELLS OF THE BLOOD

Development and Relationship of Leucocytes

Lymphocytes.—We regard the whole of the hyaline series—large lymphocytes, small lymphocytes, large mononuclears, and so-called transitionals—as belonging to one large class, which may be called lymphocytes, lymphoid cells, or lymphoidocytes, as may hereafter be found most desirable. The reasons on which we base this view are as follows:—

1. Since Wolff discovered the azurophil granules in lymphocytes we have made countless observations on their incidence in normal and abnormal conditions and we have found them in every form of the cells under discussion, from the smallest lymphocyte to the largest mononuclears and transitionals, and sometimes as numerous in the former as in the latter. The ordinary dry method is not altogether satisfactory for showing them, because, as has been shown, they are probably to a certain extent soluble in water and they always shrink considerably in dry films. The method which we have found most satisfactory for demonstrating them is to drop a film of blood on a cover-glass, before it is dry, into a weak solution of Leishman's or Wright's stain [1] in methyl alcohol, and to leave the cover-glass there for any length of time up to half an hour; then remove the cover-glass, allow it to dry, and mount in balsam. If the stain is sufficiently diluted with methyl alcohol there is no precipitate on the surface of the film, and the granules are exceedingly well brought out and are found to be larger, to be more numerous in the cells, and to be found in a larger proportion of cells than in dry films.

Pappenheim believes that these granules are not homologous with the granules of the neutrophil and eosinophil series, but that they are in some way a secretion product, and that they are contained in the meshes of the reticulum. It is extremely difficult to be sure whether this is the case or not, for a preparation which shows the granules well never shows the reticulum of the cytoplasm satisfactorily. Wright's stain or any of the stains which contain azur do not bring out the

[1] *Journ. of Med. Research*, vii. 138.

reticulum nearly so satisfactorily as Jenner's stain does, but we have sometimes seen appearances which made us think that these granules, like those of the other series, are situated at nodal points on the reticulum. Further, we have often observed them in the small pseudopodia which are thrown out by the small and large lymphocytes in blood. This is presumably more likely to occur if they are integral parts of the reticulum than if they are secretion granules.

2. It has been definitely shown that all these cells, down to the smallest lymphocytes, are capable of movement, though it is, of course, the larger cells of the class which move more actively by reason of their large amount of cytoplasm.

3. The cytoplasm of all these cells is basophil—intensely so in the smaller members of the series, less so in the larger. At Oxford in 1904[1] one of us went very minutely into this point and showed that the reason for this difference between the large and small cells is that the strands of the reticulum are not only thicker but much more tightly packed together in the small and large lymphocytes than in the mononuclears and transitionals, but that every gradation could be found between the terminal members of the series in this respect, and that it was quite common to find great variation in the character of the reticulum in different parts of the same cell, especially frequently in the cells which stand intermediate between the large lymphocyte and the large mononuclear.

4. Every transition can be found between the round nucleus of the large lymphocyte and the most polymorphous nucleus of the transitional. The fact that the nucleus does not advance further in polymorphism is probably associated with the fact that these cells are not so amœboid as the members of the neutrophil series. In some transitionals, however, the nuclers is as much twisted as in the ordinary polymorph. The bridges between the knobs of chromatin are always thicker. We have never seen anything whatever which would lead us to suppose that there was any relation between the so-called transitionals and the polymorphonuclear neutrophils.

5. The difference in size in the cells is of no great importance. It seems to us that the increase in size in the large mononuclears and transitionals is due largely to the taking up of fluid, as the strands of the reticulum are often widely separated, and these cells are obviously soft, as may be seen by the way in which they are indented in films by the red corpuscles. This œdema of the cells may make

[1] Gulland, *Brit. Med. Journ.*, September 1904.

them more labile, and we find that many of the degenerated lymphocytes in films have the appearance of mononuclears and transitionals. It is, of course, quite well known that both these larger members of the series are found in lymph glands and also in lymph from the thoracic duct and large lymph vessels.

Beattie,[1] among others, has observed many transitional forms between the different members of the series. Houston [2] believes that in normal blood it is fairly easy to distinguish between the different forms, but that this is not the case in some pathological conditions.

We are on more difficult ground when we attempt to trace exactly the relationship between the different members of the series. Pappenheim [3] regards the large lymphocyte as the mother cell which produces all other forms—red corpuscles, the cells of the granular series, and the different forms of lymphoid cells; and he regards the small lymphocyte as being older than the large cell and a riper form. This is, of course, absolutely correct as regards the reproductive history of the cells, because there is no doubt that small lymphocytes are always produced by the mitotic division of the large forms, and this occurs in lymphatic tissue throughout the body and in marrow. But he appears to consider that the small lymphocytes, when they are once formed, are not capable of further development, but that they become destroyed in blood or tissue in the same way that polymorphs are. This conclusion we are very unwilling to accept, for both in normal and pathological blood and in lymphatic tissue everywhere one finds countless cells which it is impossible to place with certainty in one or other category, and it is difficult to see whence they are derived unless it is from the growth of small lymphocytes and their conversion into larger cells. He cites in support of his view the analogue of the transformation of large megaloblasts into small normoblasts, but this is really beside the mark, because the ultimate end of the red cell is a non-nucleated non-amœboid corpuscle which has ceased to be a cell, and this cannot be said of the lymphocyte, in which, when degeneration does take place, the nucleus is the last part to disappear.

It seems to us much more probable that the ranks of the large lymphocytes are reinforced from their smaller congeners, and that further development from the large lymphocyte may take place along two lines, ending in the one case in a large mononuclear, and in the other in the

[1] Beattie, *Brit. Med. Journ.*, September 1904.
[2] Houston, *ibid.*
[3] *Folia Hæmatologica*, 1905.

so-called transitional in accordance with M. Heidenhain's[1] law as to the relative behaviour of nucleus and centrosomes in leucocytes and free cells generally. His conclusions are that the cytoplasm consists of a ground substance in which are embedded radii which have their centre in the centrosomes, astrosphere, or attraction sphere. When the

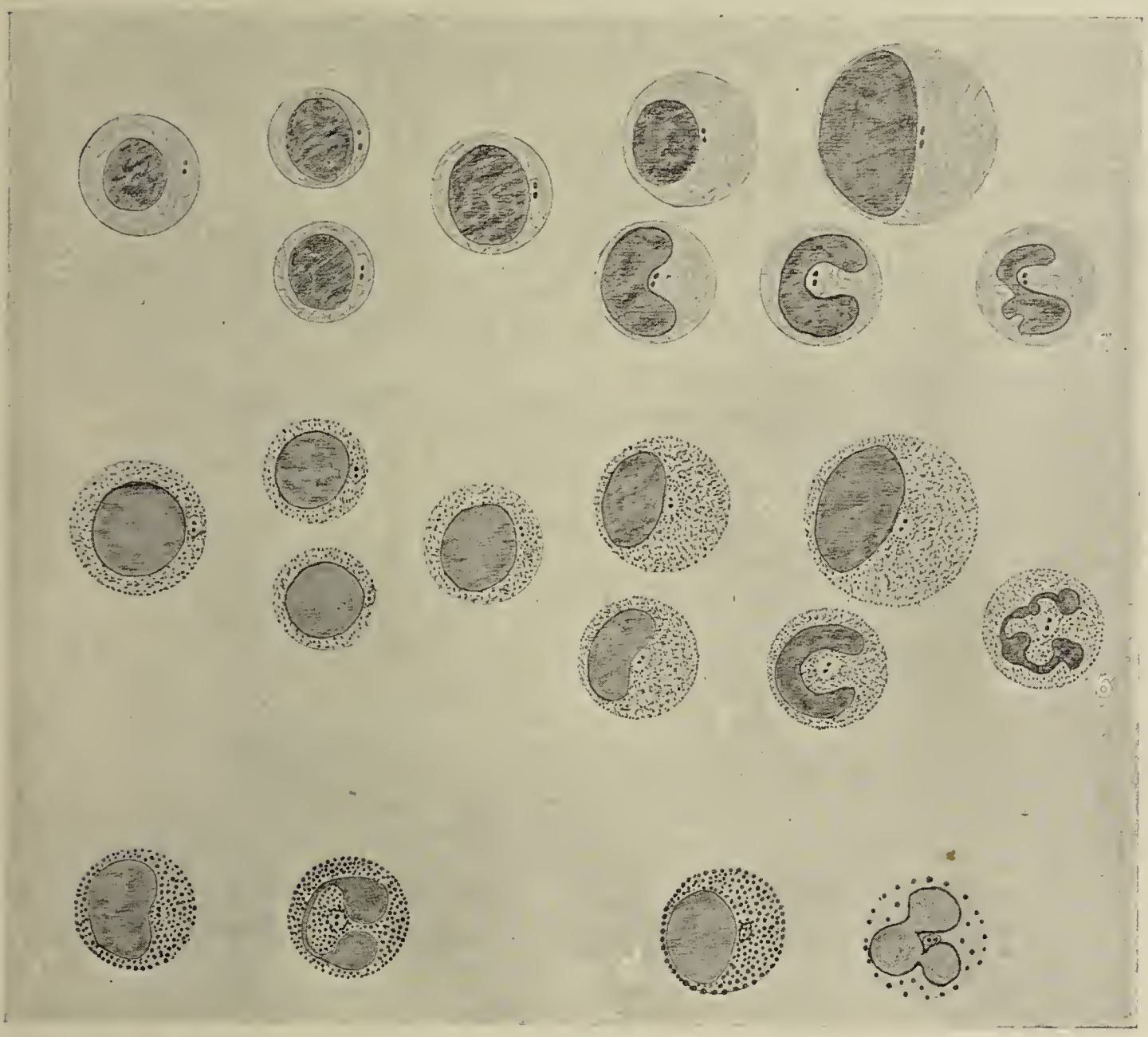


FIG. 22.—DIAGRAM ILLUSTRATING THE DEVELOPMENT OF THE NUCLEUS.

(*a*) The lymphocyte series.
1. Large lymphocyte (large lymphoid cell). 2. Daughter (small) lymphocytes. 3. Typical large lymphocyte developed by growth of 2. 4. Further development as large mononuclears. 5. As transitionals. 6. Ultimate stage of transitional.

(*b*) The neutrophil series.
1. Myelocyte. 2. Daughter myelocytes. 3. Young typical myelocyte. 4. Myelocyte corresponding to large mononuclears. 5. Myelocyte corresponding to transitionals. 6. Polymorphonuclear neutrophil.

(*c*) Eosinphil myelocyte and polymorphonuclear.

(*d*) Basophil myelocyte and polymorphonuclear.

cell is in a state of rest the pull of these radii tends to bring the astrosphere to the centre of the cell. The usual obstacle is the nucleus, and in cells with a small amount of cytoplasm, for example the small lymphocytes, the pull is not strong enough to overcome this resistance. As the cytoplasm increases in amount the pull becomes stronger and

[1] M. Heidenhain, *Arch. f. mikr. Anat.*, xliii. 1894.

the nucleus is pushed to one side of the cell and ultimately deformed, becoming first oval and eccentric, then kidney-shaped, and finally horseshoe-shaped. At this stage the astrosphere comes to rest in the centre of the cell, and a transitional leucocyte is the result. In some cells the cytoplasm grows out of proportion to the nucleus, and the astrosphere thus reaches the centre of the cell without causing any nuclear deformation. The result is a large mononuclear.

We should not like it to be understood that these two sub-series of lymphocytes are strictly separate from one another. It seems to us that, within different series, change of circumstances may result in alteration of the relations between nucleus and cell body, and that therefore a large mononuclear may conceivably be transformed into a transitional, and possibly the converse may also hold. We have already noted, however, that many of the most degenerated lymphocytes seem to be mononuclears and transitionals.

It is very difficult to find any terms which can be used instead of the objectionable terms "large mononuclears" and "transitionals." Pappenheim's proposal of "splenocytes" is unsatisfactory for many reasons. In the first place, because there is no evidence whatever (and Pappenheim himself does not suggest it) that these cells are formed specially in the spleen—in fact our researches on that organ[1] went to show that the lymphocytes which are formed in the spleen are retained entirely or almost entirely in the organ and do not pass into the blood at all. And, in the second place, there are many observations on record where the numbers of these cells in the blood remained unchanged after splenectomy. For example, Houston[2] quotes a case of splenectomy where the proportion of large mononuclears was very distinctly increased, and Crescenzi's[3] observations go to show the same thing.

The lymphocytes are the least differentiated of the leucocytes, and are found in many forms of lower animals where the cells of the granular series do not occur at all. They are the first cells to appear in the mammalian embryo (Browning[4] and others). They are, moreover, the most ubiquitous of the leucocytes. They are found in all parts of the ordinary lymphatic apparatus, in the blood, and in the bone-marrow, and in all these situations all the forms which we regard

[1] Paton, Gulland, and Fowler, *Journ. of Physiol.*, 1902.
[2] Houston, *Brit. Med. Journ.*, September 1904.
[3] Crescenzi, *Lo Sperimentale*, 1904.
[4] Browning, *Journ. of Path. and Bact.*, 1905.

as belonging to the lymphocyte series may be found, some preponderating in one situation, some in another.

Neutrophil Leucocytes.—These are known to start as leucocytes of the myelocyte form, that is, cells generally of large size with a rounded pale-staining nucleus and granules of the typical character in the cell body. The myelocytes are found normally only in the bone-marrow. In pathological conditions myelocytes may be found, not only in the marrow but in all the hæmopoietic organs, including the liver. This myelocyte form divides by mitosis; the resulting cell is rather smaller than the mother myelocyte, but otherwise similar in character. It grows by enlargement both of the nucleus and of the cell body, and its nucleus may remain rounded, especially in cases where the cell body rapidly increases in size, or may become indented, kidney-shaped, and ultimately horseshoe-shaped or even ring-shaped. The nucleus of the ripe neutrophil cell may assume almost any shape, and it has, moreover, a tendency to be made up of knobs of chromatin joined together by narrow bridges. We would remark, however, that our ordinary methods of film preparation make the narrowness rather more marked than it should be. Wet preparations made by our sublimate-alcohol-ether method, or in other ways, show a much more compact nucleus as a rule, with thicker bridges between the knobs.

This progression from the rounded form to the polymorphous nucleus is in full accordance with M. Heidenhain's law as explained in relation to the lymphocyte series. As the centrosome is pulled towards the centre of the cell, the nucleus is pushed to one side and ultimately deformed, becoming first oval and eccentric, then kidney-shaped, and finally horseshoe-shaped. At this stage the astrosphere comes to rest in the centre of the cell, and even with ordinary methods the clear space free from granules, which represents the astrosphere, can often be seen lying in the hollow of indented or kidney-shaped nuclei. In some cells the cytoplasm grows out of proportion to the nucleus, and the astrosphere thus reaches the centre of the cell without causing any nuclear deformation. Many of the large myelocytes have this shape.

We have been accustomed to consider that after a cell with a horseshoe-shaped or ring-shaped nucleus begins to move the nucleus moves with it, and may be secondarily deformed, and the more amœboid the cell the greater is the deformation likely to be. For this reason the nuclei of the neutrophil polymorphous form were supposed to be so much more deformed than those of the eosinophil polymorphous form,

because they are more actively amœboid. But a very acute paper by Pappenheim[1] puts this process in another light, and gives a much better explanation. He points out that polymorphism of the nucleus is not an expression of the power of locomotion, nor of active kinetic locomotion, as on the one hand mononuclear cells may also be amœboid and remain mononuclear during that process. Such cells are the mast-cells of connective tissue, the primary wandering cells, the small lymphocytes of the blood, and others. On the other hand, polymorphous nuclei remain polymorphous when the cell is entirely at rest, as in the ordinary neutrophils of the blood. The myelocytes are also mobile, but the changes in the nucleus produced during their movements are quite different from polymorphous nuclei. Polymorphism is really an internal plastic process, the expression of a change in the internal structure of the cell, and really a process of ripening. He agrees with the observations of M. Heidenhain, which we have already cited. We would be inclined to go a step further and to consider that the nucleus becomes polymorphous in order that the cell may become more actively amœboid. There is ample evidence that the power of amœboid movement lies in the cytoplasm and that the nucleus is passive, and, indeed, except for its relation to the life of the cell, rather a hindrance to movement. Therefore the more the nucleus is broken up into lobes with narrow bridges between them the easier will it be for the cytoplasm to drag it through narrow openings.

Pappenheim also considers that these changes of plastic ripening cannot be turned back, and that though in suppuration and, for instance, in sputum one often finds mononuclear neutrophil and eosinophil forms, these are easily distinguished from normal mononuclear forms or myelocytes.

The actual form of the neutrophils varies in different animals, and perhaps in relation to mammalia generally it would be better to use the term "oxyphil" rather than neutrophil. They are confined to warm-blooded animals.

Eosinophils.—The eosinophils also start as myelocytes. These are found in the bone-marrow, but also to a certain extent in connective tissue, thymus, lymphatic glands, and elsewhere, though it is doubtful whether they multiply in these situations to any very great extent. Like the neutrophils they may be found in any of the hæmopoietic organs in pathological conditions.

[1] Pappenheim, *Folia Hæmatologica*, ii. 1905.

The series is phylogenetically next in age to the lymphocytes, and one finds that these cells appear in many cold-blooded animals, and that they occur in mammalian embryos at a date not very much later than the lymphocytes but long before the neutrophil series. They are not quite so ubiquitous as the lymphocytes, but they are certainly found with great frequency in connective tissue without any very evident reason for their presence, and it seems probable that they may multiply in these situations, from the fact that myelocyte forms are often found. They are probably produced mainly in the bone-marrow, because it has been shown that in cases where there is a marked blood eosinophilia the number of myelocyte forms in the marrow is very greatly increased; but they seem capable of considerable adaptation to other conditions, and in cases where the marrow is rendered unsuitable for their proliferation, as in some lymphatic leukæmias, they are found in numbers in the spleen, liver, and elsewhere, sometimes in company with neutrophil myelocytes, but much more frequently, and apparently earlier, without them.

In these two granular series it is to be noted that only the final polymorphonuclear forms are to be found in the blood in normal conditions. All the precursors of that stage are found normally only in the marrow, with the possible exceptions in the case of the eosinophils already noted. It is fully agreed that a demand for polymorphs of either of these series in the blood or in the tissues results in an increase in the number of myelocyte forms in the marrow, and if the demand for cells is sufficiently great, results in an increase in the amount of functional marrow.

Basophils.—With regard to the basophil series the evidence is not quite so complete. These forms are very scanty in either normal or pathological blood, with the single exception of splenomedullary leukæmia and a few other conditions in which experimentally it has been shown that they can be increased. The presence of myelocyte forms in the marrow and polymorphonuclear forms in the blood makes one conclude that their development is along similar lines to that of the other granular cells.

The Relation of Leucocyte Forms to One Another.—From what has just been said with regard to the ancestral character of the lymphocyte and from all that is known of its history it is obvious that it is the primary form of all leucocytes, so far at least as embryonic life is concerned. An immense amount of discussion has raged over the question

as to whether the same can be said of lymphocytes in post-embryonic life—whether they form an absolutely independent series or whether the other series spring from them. From everything that is known with regard to the facts of chemiotaxis and leucocyte response we think one must conclude that for practical purposes the different series are kept apart in adult life. Under ordinary conditions certainly mitotic reproduction of myelocyte forms is quite sufficient to supply ordinary needs.

Much has been written about the occurrence of eosinophils and neutrophil myelocytes with basophil cytoplasm (*promyelocytes*), and these have constantly been quoted as transitions from lymphocytes to the other forms. We think it would be impossible for us to deny the possibility of such a thing occurring. What has happened in embryonic life may, under certain conditions, occur again. The existence of pernicious anæmia is a sufficient answer to the objections to this view, but it must also be remembered that in judging of the nature of these cells all young cells tend to have basophil cytoplasm, and these forms may be simply freshly formed myelocytes.

There is a strong tendency at the present time to distinguish the primitive cells of the granular series (*myeloblasts*) from those of the lymphocyte series. The distinction is based upon the nuclear characters described on p. 68, the intensely basophil characters of the protoplasm, and a positive oxydase reaction. From the developmental aspect the point is not of great importance, since (as Muir puts it) it is merely a question of the stage at which characteristic differentiation begins. A matter of more importance is the occurrence of myeloblasts in leukæmia. Here we are met with the difficulty that only by the use of panoptic stains can the special characteristics of myeloblasts be shown, and even then the existence of transitional forms between lymphocytes and myeloblasts will cause much difficulty. It has further been shown that a sufficiently primitive myeloblast does not give the oxydase reaction—a negative characteristic which it shares with the lymphocyte.

The Relation of Leucocytes to Red Corpuscles.—If one goes far enough back in embryonic life one reaches a stage at which there are no true leucocytes and no true nucleated reds, but only undifferentiated cells which may become either one or the other, and in this sense it is possible to say that leucocytes and red cells start from a common origin. One set of these cells acquire or manufacture hæmoglobin in

their cytoplasm and become the megalobastic precursors of ordinary red cells; the other sets do not come to contain hæmoglobin and become the precursors of the leucocytes (*cf.* Bryce[1]). The former cells multiply in mammalian embryos with extraordinary rapidity, while the latter remain almost stationary in number for a long period. It is thus easy to find stages in development at which the nucleated red cells outnumber the leucocytes in the embryonic body by thousands to one, and where the red cells are actively dividing while the leucocytes are not observed to be doing so. It would seem absurd at such a stage to talk of the derivation of red cells from leucocytes, and if this is the case at so early a stage of development, when both sets of cells are comparatively undifferentiated, it would seem still more idle to suppose that in adult life there can be relationship between the two. No author has attempted to connect any series of leucocytes with red cells other than the lymphocyte.

One fails, indeed, to see why nucleated reds should be supposed to be formed from lymphocytes. If it be granted that erythroblasts can and do multiply by mitosis, which nobody doubts, and if they have a suitable locus for development as they have in the bone-marrow, there is no reason whatever to suppose that their activities require to be reinforced by the lymphocytes under ordinary conditions. The conditions in lymphatic leukæmia alone might be cited as a sufficient argument against this view. We have gone over many marrows in this condition in acute cases in which the red count had fallen steadily as the white count rose. These marrows had undoubtedly been subjected to a functional stimulus and were full of large lymphocytes, but we had often to search long and carefully before we could find a nucleated red of any kind. The lymph glands in these cases were either normal or infiltrated with lymphocytes, but contained no nucleated reds outside the blood-vessels. Surely in these cases where the patients were dying of anæmia, if in any, the hypothetical transformation of lymphocytes into erythroblasts ought to have been going on. But we could never see the slightest evidence of it; indeed, the lymphocytes were often much too busily employed in devouring red cells to have any time to spare for the making of them.

The Source of the Lymphocytes in the Blood.—We have been led to take an interest in this from the experiments which we have made as regards digestion leucocytosis.[2] In animals we found that

[1] Bryce, *Trans. Roy. Soc. Edin.*, 1904.

[2] Goodall, Gulland, and Paton, *Journ. of Physiol.*, xxx. 1903.

the rise was due largely to an increase in lymphocytes which was constant, and to a rise also in the polymorphs which was not so constant but might reach a higher figure. We succeeded in eliminating the intestinal mucous membrane, the spleen and the mesenteric glands, as causes of this increase, and Goodall and Paton[1] have since shown that the source of these lymphocytes is the bone-marrow. Their experiments prove that the actual number of lymphocytes passing into the blood from the thoracic duct is comparatively small—much smaller than one would have expected; and that it in no way accounted for the very great increase of lymphocytes in the blood. On the other hand, the blood coming from the marrow was shown to be very much richer in lymphocytes and in polymorphs during digestion.

Many other observations are now on record which go to prove that the thoracic duct is not an important source of lymphocytes in the blood, though of course it undoubtedly does carry a certain number thither. The experiments of Crescenzi[2] are of great value in this respect. After splenectomy and drainage of the thoracic duct it was found that the lymphocytes dropped rapidly for the first day or so, as one often finds to be the case after an operative procedure in animals. But after one to four days the lymphocytes returned to the normal point or rose above it. Crescenzi considers that this is due to a direct passage of lymphocytes into the blood from the lymphatic tissue, because he found that the marrow histologically showed no compensatory proliferation, and that there was no new formation of collateral lymph paths; but it seems to us that his experiments show that the marrow was in reality producing lymphocytes actively all the time, and of course no compensatory change was necessary.

The large mononuclears and transitionals showed no constant change after these operations; they were sometimes increased, sometimes diminished. Our own experiments on the function of the spleen showed pretty definitely that that organ was not an important source of lymphocytes, and the experiments of Azzurini and Massart[3] have confirmed this.

Further, there is now no doubt whatever that a large number of lymphocytes are actually present in the marrow. The observations of Pappenheim, Price Jones,[4] Longcope,[5] and our own repeated observa-

[1] Goodall and Paton, *Journ. of Physiol.*, xxxiii. 1905.
[2] Crescenzi, *Lo Sperimentale*, 1904.
[3] Azzurini and Massart, *Lo Sperimentale*, 1904
[4] Price Jones, *Brit. Med. Journ.*, February 1905.
[5] Longcope, *Centralb. f. Bact. u. Paras.*, 1904.

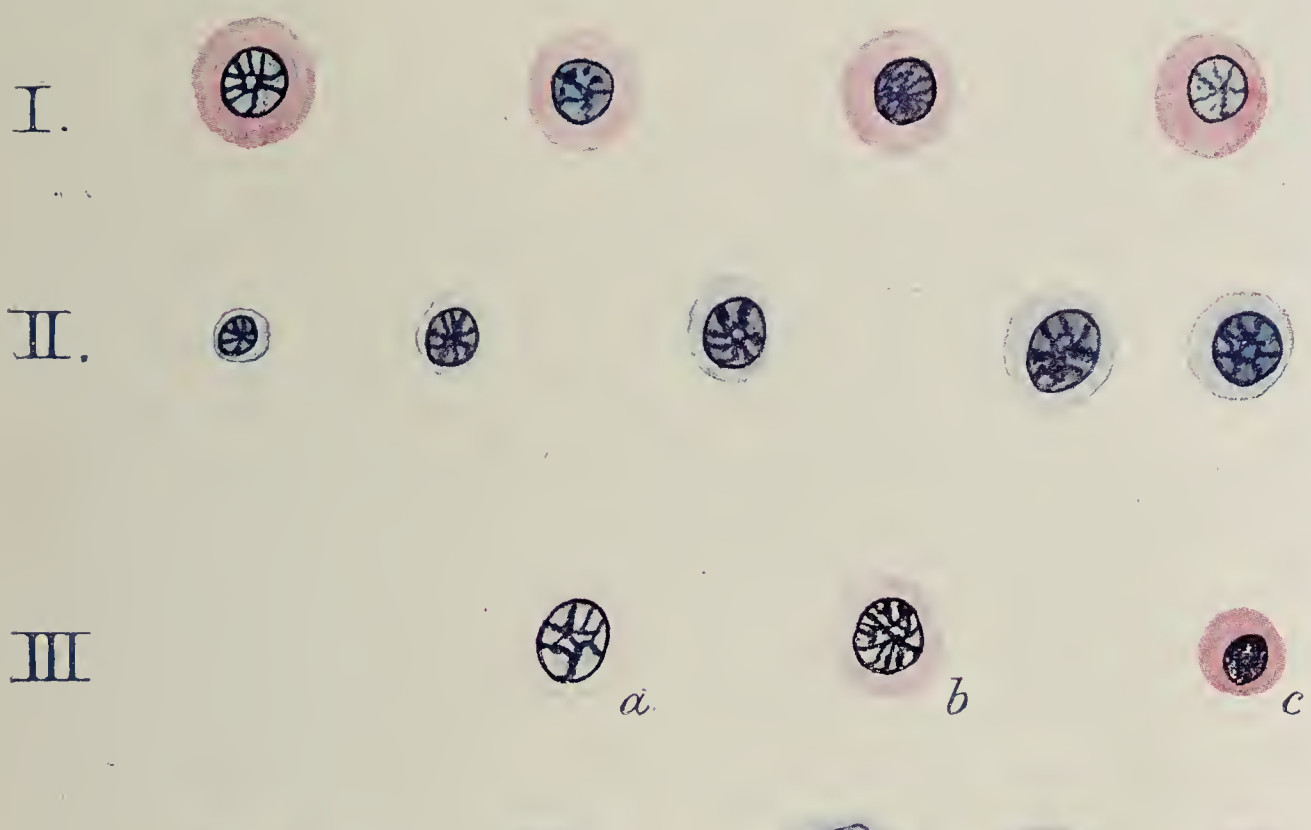


PLATE V.—HÆMATOGENESIS.

I. Primitive megaloblasts.
II. Non-hæmoglobin-containing erythroblasts from fœtal liver.
III. *a*, *b*, Young polychromasic megaloblasts; *c*, a normoblast.
IV. *a*, Primitive leucocyte developing as a giant cell.
V. Development of the primitive leucocyte as (*a*) a promyelocyte; (*b*) a young myelocyte; (*c*) an older myelocyte; (*d*) a polymorphonuclear neutrophil.
VI. Development as (*a*) an eosinophil myelocyte; (*b*) an eosinophil polymorph.
VII. Development as (*a*) small lymphocytes; (*b*) large lymphocyte.

A. G., *fecit*.

tions have put this beyond doubt. Longcope found in the marrow, under normal conditions, 22 to 23 per cent. Again, there are certain diseases where there is a marked chemiotactic passage of lymphocytes into the blood from the marrow—in whooping-cough and smallpox in particular, and possibly in typhoid also.

Development of the Red Cells

(a) *In Fœtal Life.*—The primitive red blood-cells are nucleated (megaloblasts) (Plate V., 1). They are first produced by a modification of mesoblast cells in the vascular area surrounding the early embryo. They are then found proliferating in the fœtal vessels before any hæmopoietic organ is developed. Great numbers show mitosis. But a time soon comes when this stock is insufficient to maintain the necessary supply of cells and at the same time carry on respiratory function. As soon as the liver is developed a new set of cells arises. They are found between the islands of liver cells. These are erythroblasts which do not contain hæmoglobin. The absence of hæmoglobin is to be accounted for by the fact that the cells are stationary and have no respiratory function, and therefore do not require it. It is also probable that hæmoglobin may be a hindrance to the process of mitosis. It is an open question whether these cells are derived locally from undifferentiated mesenchyme cells or from the circulating hæmoglobin-containing megaloblasts.

Bryce discusses this question in connection with the spleen in his researches on *lepidosiren,* and concludes for the former alternative, for the reason that the number of erythroblasts is out of proportion to the number of megaloblasts showing mitosis, and for the more cogent reason that the nucleus of the erythroblast differs from that of the primitive megaloblast.

The question is difficult, but we conclude for the alternative that the erythroblasts are the direct progeny of the first megaloblasts.[1] We can distinguish no difference in nuclear structure, and for the reasons just indicated there can be little doubt that the erythroblasts can and do proliferate much more rapidly than the first megaloblasts. The erythroblasts having arisen may proliferate for many generations without hæmoglobin, or may begin to acquire it almost at once. Mitosis may occur in these hæmoglobin-containing cells (second megaloblasts), which are indistinguishable from the first megaloblasts

[1] Goodall, *Journ. of Path. and Bact.*, 1908.

found before erythroblasts are developed. This, however, is uncommon as compared with erythroblast division.

The presence of megaloblasts with their nuclei undergoing degeneration and absorption becomes a common appearance, and even at a fairly early stage in fœtal life the great majority of the blood corpuscles in the circulatory system are non-nucleated. The proportion of nucleated cells in the circulation does not represent the activity of proliferation, and their presence is probably not so much due to the proliferation as to the disturbance of the reticulum of the hæmopoietic organs which the proliferation causes.

By mid-term many of the nucleated red cells have a nucleus of the normoblastic type. Thereafter normoblastic blood formation increases at the expense of the megaloblastic, with the result that in course of time the majority of the circulating red corpuscles are normocytes and not megalocytes.

Megaloblastic blood formation persists not only to the end of but for some time after fœtal life. It is indeed likely that it never entirely disappears. It does not follow that megalocytes are supplied to the circulation. The megaloblasts give rise to normoblasts; the normoblasts in their turn give rise to erythrocytes. The latter process consists in the internal disintegration and absorption of the nucleus. The old view that the normoblasts give rise to erythrocytes by extrusion of the nucleus is now almost entirely given up. A normoblast with a partially extruded nucleus may occasionally be seen, but the extrusion is brought about in the process of manipulation.

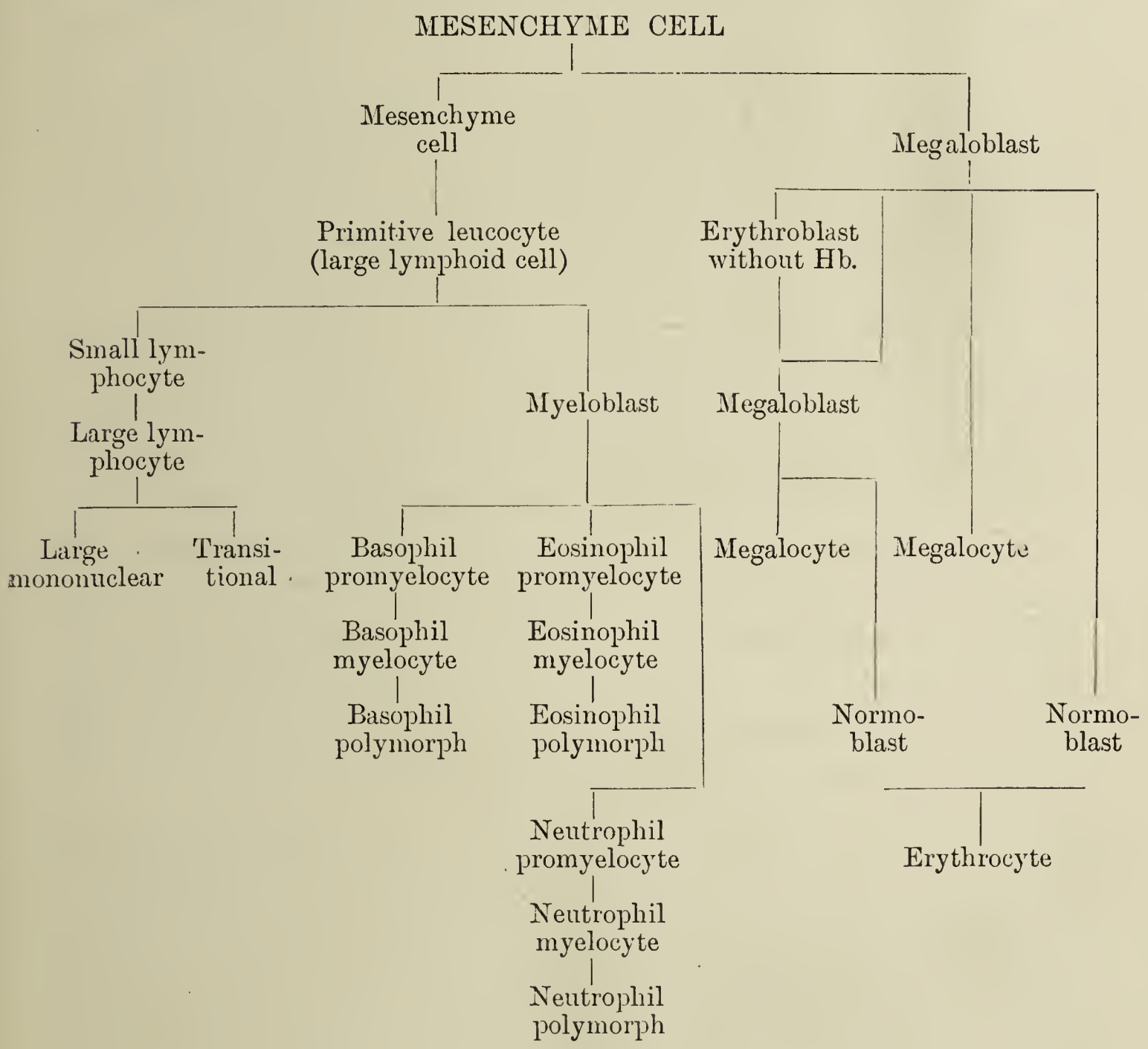
When the spleen is developed it takes part in the process of hæmatogenesis, but as soon as the marrow is formed the process goes on more actively there. In later fœtal life the hæmopoietic activity of the liver and spleen greatly diminishes and terminates altogether rather abruptly at or about the time of birth. Meantime the marrow has increased greatly in amount, and becomes the only source of the red cells supplied to the organism.

(b) *In Post-Natal Life.*—The source of the red corpuscles is the bone-marrow only. They are derived from normoblasts which proliferate in response to the needs of the body. The nucleus is absorbed before the cells escape into the circulation. In pathological conditions such as pernicious anæmia and leukæmia proliferation of red cells may again take place in the liver and spleen and even in the peripheral circulation.

A certain number of cells of the fœtal type remain in the bone-

marrow in later life. The megaloblast and its non-hæmoglobin-containing progenitor remain as non-circulating elements, and under abnormal conditions may proliferate to such an extent that megalocytes and megaloblasts appear in the circulating blood. In the same way the primitive leucocyte remains a normal constituent of the bone-marrow and retains its potentialities of producing all the members of the white cell group. Under ordinary circumstances it is probably not called upon, any more than the surviving megaloblasts are called on. The sequence of ordinary development goes on in each series separately, but in such extreme pathological disturbances as leucocythæmia the primitive leucocyte may play a very important part.

The following scheme summarises the genealogy of the red and white cells:—



LITERATURE.

Fränkel, *Folia Hæmatologica*, *Archiv* xvii. 1913, p. 1, gives a historical résumé and numerous references.

PART III

DISEASES OF THE BLOOD AND BONE-MARROW

CHAPTER XIV

PERNICIOUS ANÆMIA

Definition.—A disease characterised by severe anæmia of megaloblastic type.

Etiology.—*Age.*—The disease is most common between thirty and fifty, though no age seems exempt. It is very rare in children. Hutchison, in 1904, collected eleven cases from the literature, and of these only five appeared to him to be genuine. Cases in old age are much more common.

Sex.—Curious differences exist between the statistics which have been published. German statistics show a considerable preponderance of the disease among females. American records, on the other hand, indicate that the disease is more common in males. Our experience is in accordance with the latter. Out of a series of 500 cases which we have seen 171 were females. Social conditions have no influence. The disease is common among the well-to-do.

Heredity seems sometimes of importance. It is quite common to get a history of one other case in a family. In one of our cases the patient's father, paternal uncle, brother and sister had all died of the disease; in another the patient's father, uncle, and sister had died of it.

A host of depressing conditions and other diseases have been suggested as causal agents in pernicious anæmia, and in individual cases may be of importance. The great majority of these are at least not proven, but a certain proportion of cases begin during pregnancy or the puerperium, a few cases have followed cancer of the stomach (though secondary anæmia is infinitely more frequent), and cases are sometimes due to bothriocephalus infection. We have noticed a relatively large incidence among plumbers, men employed in gasworks,

and other occupations involving the breathing of impure air. Sewage gas has been suggested as a cause, but we have repeatedly seen cases in which the patients lived in isolated houses in the country, where this was out of the question. Others have followed syphilis or malaria. In the great majority of cases no history of any causal factor can be ascertained, and dyspepsia, usually of a vague and ill-defined character, is the only condition which can be said to precede it with any constant frequency.

Morbid Anatomy and Histology.—The pallor of the body in a case of death from pernicious anæmia is very striking. There is generally a slight icteric tinge. Post-mortem lividity is very slight, and may be absent. The subcutaneous fat is well preserved. There is intense anæmia of all the organs. Hæmorrhages may be noted in the skin, mucous or serous membranes. They are fairly frequent in the meninges.

The Tongue.—Attention has been directed to smooth, atrophic-looking areas on the tongue during life (Hunter). We have been unable to find any microscopic change to account for these appearances, which seem to be due to a physical condition of the superficial layers of the epithelium.

Stomach and Intestines.—A great variety of lesions have been described. Among these are atrophy and thinness of the coats of the intestine, smoothness of the mucous membrane and atrophy of glands, and overgrowth of lymphoid tissue.

Faber and Bloch pointed out that the apparently atrophic changes were in large measure due to post-mortem change, and stated that they were not found if the abdomen were injected with formaline immediately after death.

This observation we have been able abundantly to confirm. In some cases there is certainly some degree of gastric and intestinal atrophy, but no more than is to be found in many chronic diseases. Hæmorrhages are sometimes seen in the mucous and serous coats. Occasional ulcers may be noticed in the bowel, but with no special frequency. In the submucosa we have found constantly curious basophil cells, some of them containing enormously large granules which may greatly distend the cell and whose individual size may be greater than that of a red blood corpuscle.

Liver.—The liver is always fatty. There is always a considerable amount of pigmentation. This, for the most part, is seen towards the

periphery of the lobules. This pigment has a golden brown colour, and most of it gives the free iron reaction. Iron is seen in the liver cells, but also in endothelial cells and in free phagocytic cells in the capillaries. A further change in the liver is the presence of necrotic-looking areas, usually in the middle zone of the lobules. Between the rows of necrotic liver cells the capillaries are widened, and in the dilated capillaries are numerous nucleated red cells (megaloblasts and normoblasts) and phagocytic cells containing red corpuscles or pigment. The latter may give the iron reaction, and in a few cases so completely that the whole cell becomes blue when the ferrocyanide test is applied. Giant cells resembling those of bone-marrow are to be seen in these areas in the majority of cases.

Spleen.—No marked or constant change is to be found in connection with the Malpighian bodies. The pulp shows considerable variation as regards the kind of cell preponderating. In most cases there is congestion, and normoblasts and megaloblasts in varying numbers are present. In a few cases lymphocytes definitely preponderate in the pulp. At least half the cases show large giant cells ingesting red corpuscles, and sometimes also white cells; giant cells resembling those of bone-marrow are sometimes seen. In a few cases there are numerous basophil cells in the pulp, and some of these show the dropsical appearance seen in those of the intestine. Pigment is present in varying amount in all cases. Usually a certain proportion of this gives the iron reaction, in some cases in very large amount. The pigment is found free in the pulp, or in leucocytes or endothelial cells.

Kidneys.—In nearly every case there is catarrhal or interstitial nephritis, the former probably toxic in origin, the latter probably pre-existing, and in many cases granules of pigment giving the iron reaction are seen in the epithelium of the convoluted tubules, sometimes in very large amount. This iron pigment is found more frequently in cases terminating acutely than in those of chronic type.

Heart.—In the great majority of cases the heart muscle shows fatty and other degenerative changes, though not in an extreme degree. These are sometimes absent. In typical cases of fatty degeneration the familiar "thrush's breast" appearance may be seen on the endocardial surface of the ventricles in particular.

Lungs.—There is no special feature associated with the disease, but patches of catarrhal pneumonia are extremely common, and many cases terminate with croupous pneumonia.

Hæmolymph Glands.—These are generally numerous, large, and dark

red in colour, and are most numerous and largest immediately in front of the vertebral column in the lumbar region, especially the lower part of it. They show very great hæmolytic activity, red cells being ingested by large phagocytes in great numbers. Pigmentary changes are not so marked as might be expected, and only a small proportion of the pigment present gives the free iron reaction.

The Bone-Marrow.—The bone-marrow throughout the body is dark red in colour and increased in amount. The ordinary fatty marrow has disappeared and there is a very considerable absorption of bone, so that the medullary cavities are considerably enlarged.

The striking feature of sections and films is the very large number of megaloblasts which are seen. In no other condition are they so numerous or so large. Normoblastic activity is also very great. In some cases basophil degeneration of the red corpuscles, particularly of the nucleated reds, may be noticed, but it is not nearly so frequent as one would expect from its incidence in the circulating blood.

There is always a larger proportion of white cells than might be expected from the leucopenia in the blood. Considering the vast increase in the amount of active marrow in this disease, the number of marrow leucocytes must be very greatly in excess of the normal. In view of this it is difficult to explain the constant leucopenia and the rarity of leucocytosis, even in the presence of severe septic complications, unless one assumes that the toxin or toxins causing the disease in some way interfere with the passage of leucocytes into the blood, or with the transformation of myelocytes into the polymorphonuclear form. It is to be noted that the number of polymorphs in the marrow is always small—much smaller than in a normal marrow. In nearly 50 per cent. of cases white cells appear more numerous than the red cells. Those present are mainly myelocytes or lymphocytes. They may be present in about equal proportions, but as a rule one or other preponderates, and the one variety preponderates just as often as the other.

Eosinophil cells are seldom numerous. Basophils are present in considerable numbers in a small proportion of cases. Giant cells are small and degenerated, very seldom normal.

There is generally marked evidence of blood destruction, as shown by phagocytosis of both red and white cells. Pigment, free or intracellular, showing the free iron reaction is found in about one-third of the cases.

The Nervous System.—Recent or organised hæmorrhages are practi-

cally always to be seen in the membranes. In the very few instances in which a histological examination of the brain has been made there have been small hæmorrhages in the brain substance and some indications of impaired nutrition of the brain cells.

Observations on the cord have been more numerous. Small hæmorrhages are usually found. The vessels are often dilated and show hyaline degeneration. There are small foci of degeneration in the white matter in the vicinity of vessels. These may run together to form large areas of sclerosis, and may thus give rise to secondary degeneration of the nerve tracts. Combined postero-lateral sclerosis is the common lesion. Sclerosis may also be seen in the gray matter, though it is not so common. Nissl's granules may stain imperfectly, the nucleoli may be swollen, and the protoplasm of the cells pigmented. The lesions are more common in the upper part of the cord than the lower.

The peripheral nerves often show indications of neuritis.

Relationship of Pathological Appearances to Clinical Features.—In this connection we find—

1. The necrotic areas in the liver are more marked in the more chronic cases.

2. The more acute cases show more iron in the liver, spleen, and kidney, and in the more chronic cases a considerable amount of pigment, which does not give the iron reaction, is present.

3. There is a striking relationship between the acuteness of the case and the number of megaloblasts both in the blood and in the marrow.

4. The cases which have shown most megaloblasts in the blood show most megaloblasts in the bone-marrow.

5. There is no necessary relationship between the differential leucocyte count of the blood and the marrow type. In practically all cases the blood shows leucopenia with a relative lymphocytosis.

Pathology.—At the outset we may state that the fatty and other degenerative changes in the heart, the fatty changes in the liver, the catarrhal and sometimes also the interstitial changes in the kidney, the fairly frequent patches of pneumonia, and the nervous lesions, seem to throw no light on the pathology of the disease, but, when not pre-existing, are secondary to the severe anæmia or to its cause.

Alimentary Canal.—Much diversity of opinion exists regarding the importance of the changes found.

We are inclined to think that, with the exception of the presence of

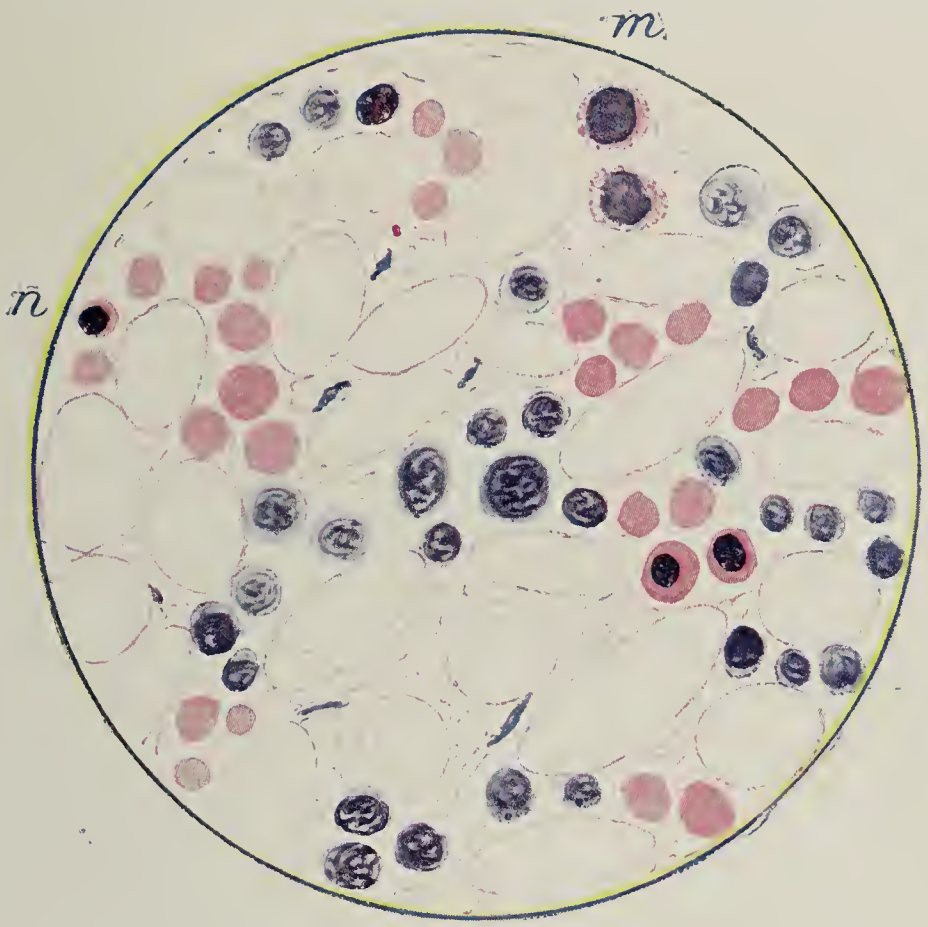


FIG. 1.—APLASTIC RED BONE-MARROW.

Blood-cells are scanty. Only three normoblasts (*n*) and two myelocytes (*m*) are present. The section shows mainly fat-cells and lymphocytes.

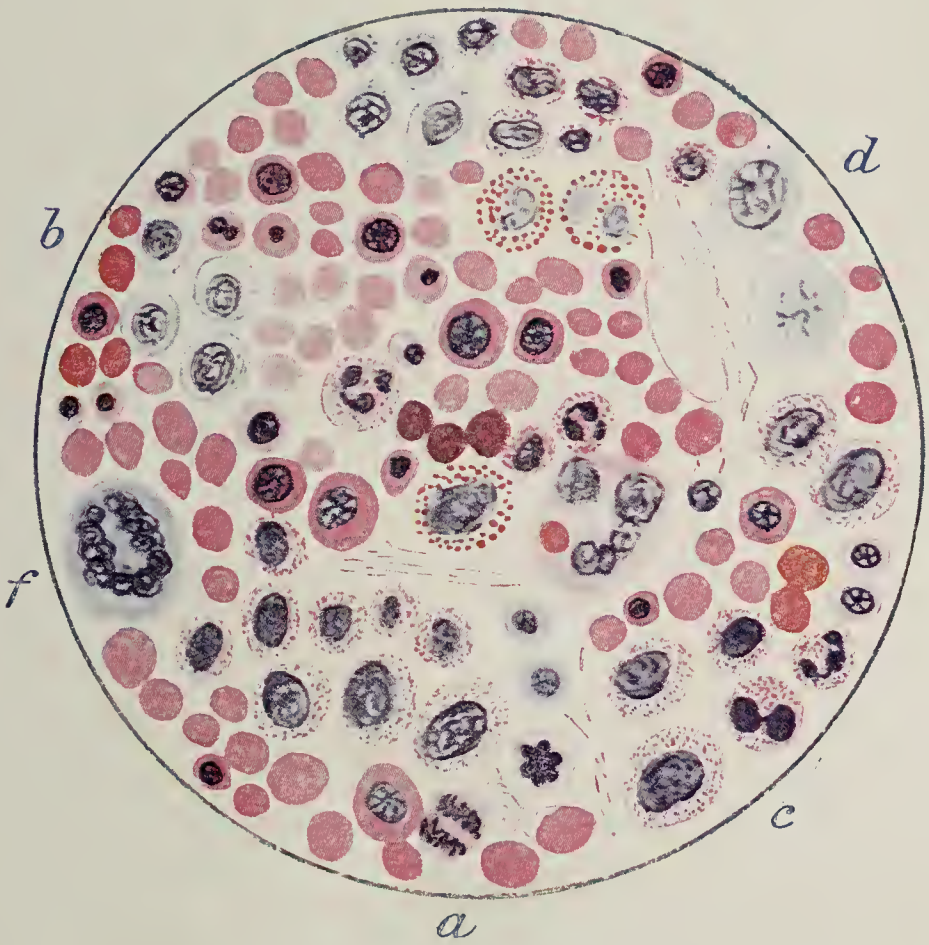


FIG. 2.—MARROW FROM CASE OF PERNICIOUS ANÆMIA.

There are numerous megaloblasts (*a*), some showing mitotic figures. There are also normoblasts (*b*).
Myelocytes (*c*) are numerous, as are lymphocytes (*d*). There are a few eosinophils.
There are two giant cells, one young (*f*) with basophil protoplasm, another older with acidophil protoplasm showing an ingested red cell.
Only one fat-cell is present in the whole field.

A. G., *fecit*.

basophil cells as described, the appearances found by us in the stomach and intestine could be summed up as "post-mortem" change.

Liver.—The large amount of iron in pernicious anæmia is a striking feature. Our observations lead us to believe that this accumulation is due to two factors—(*a*) storage, and (*b*) hæmolysis.

(*a*) By far the greater part, namely, that in the liver cells at the portal periphery, is simply stored up, the liver being the normal channel for the excretion of products of broken-down hæmoglobin. This accumulation is greater in the more acute cases, because the amount of iron brought to the liver must be largely in excess of the usual rate of elimination.

We do not look upon this iron as indicative of anything more than mere storage. It is specially marked in pernicious anæmia, because of prolonged accumulation, but it is not pathognomonic, and we have seen more iron in the liver in cases of acute lymphatic leukæmia than in the average case of pernicious anæmia.

(*b*) Altogether apart from this more or less passive storage, we find a certain amount of active hæmolysis of the same character as that seen in the spleen, hæmolymph glands, and marrow, namely, iron contained in endothelial cells, and red cells and pigment contained in large phagocytes. These appearances have been found to predominate over the passive accumulation in the liver cells in animals in which sudden blood destruction has been caused by the injection of hæmolytic agents.

We find that the amount of iron and other pigment in endothelial cells in the liver is greater in the acute cases. This would mean that the liver in acute cases is obliged, as it were, to deal with large quantities of the first products of the disintegration of weakly or weakened red corpuscles, or the corpuscles themselves, while in the more chronic cases these products are, for the most part, brought to it in a state more suitable for storage. The passive accumulation of iron frequently obscures the more active hæmolytic process, but we have seen examples of the usual storage at the periphery of lobules, while towards the middle and central part of the lobule there was hæmolytic accumulation of iron in the endothelial cells. It is not unreasonable to assume that the megalocytes of pernicious anæmia, which are so definitely fœtal in their characters, are ill adapted to the needs of adult life, and probably have a shorter existence in the blood-stream than normal red corpuscles.

The necrotic areas which we have described are most marked in the

mid-zone of the lobules, and are usually confined to that situation. In the more chronic cases they extended out to the portal zone.

The presence of a considerable number of red cells, often nucleated, and giant cells indistinguishable from those of bone-marrow, is suggestive that in some cases the liver may revert to its fœtal function of blood formation. It is, of course, well known that the wide capillaries in the fœtal liver are the site of blood formation at a stage of development before the bone-marrow is formed. These capillaries then contain numbers of giant cells, nucleated red corpuscles, and leucocytes of various kinds. The fact that these widened capillaries in the liver are more evident in chronic cases of pernicious anæmia suggests that in them the whole available marrow has been transformed into erythroblastic and leucoblastic tissue, and that the marrow function has overflowed into its old channels. This overflow recalls in a very striking way the analogous condition of deposits in the liver and elsewhere in long-standing cases of leucocythæmia. The absence or slighter amount of the change in the acute cases may be taken to mean that there has not been time for it to occur, or that there has not been a sufficient power of proliferation in the marrow to permit of its occurrence.

It is probable that the necrotic areas are due to pressure and interference with liver function from the accumulation of cells possibly engaged in blood formation, and cells engaged in phagocytosis in the capillaries between them.

On the other hand, it might be that the necrotic areas are due to absorption of toxins from the intestine, but against this view is the fact that they are more marked in the more chronic cases.

The fatty changes are secondary to the anæmia.

Spleen.—We now know that the spleen does not play any very important part in normal hæmopoietic processes. Its main function appears to be the removal of old or damaged erythrocytes from the circulation, and we have no reason to think that its rôle in pernicious anæmia is different. The occasional presence of basophil cells with large dropsical granules might suggest some localisation of toxin, as in the case of the intestine and bone-marrow.

As in the liver, the presence of bone-marrow-like giant cells in some cases makes it seem probable that in prolonged cases the spleen attempts to meet the demand for erythrocytes by returning to its fœtal hæmatogenic function.

Hæmolymph Glands.—The changes simply indicate very active per-

formance of the normal hæmolytic function, chiefly by the action of large phagocytes derived from leucocytes and endothelium.

Bone-Marrow.—In every case the naked-eye change is identical, and although the microscopic picture varies according to the kind of cell which preponderates, the changes are essentially the same. There is undue activity of red cell and white cell formation, and the former assumes the megaloblastic or fœtal type. The hæmolytic changes are similar to those found in other organs.

All our observations tend to convince us that this is the essential seat of the disease. If the bone-marrow changes be secondary and some other symptom-complex be primary, would it not be reasonable to expect to see cases clinically before the bone-marrow is affected, and consequently before megaloblasts and megalocytes were to be found in the blood? And if we exclude the blood and bone-marrow changes as essential and primary features, what is the criterion in diagnosis, and why should we call the condition pernicious "anæmia"? We are not in agreement with those observers who hold that the marrow changes are secondary phenomena.

We know of no symptom-complex apart from the blood changes or of any morbid appearance apart from the marrow changes which could be regarded as exclusively distinctive of pernicious anæmia.

The changes are due to exhaustion of the bone-marrow, or interference with its functions, by the action of toxins. It is not necessary to assume that these toxins are in all cases the same.

The condition can be caused by bothriocephalus infection, malaria, syphilis, gastric carcinoma, and probably many other conditions, and the essential features are due rather to the affection of a definite tissue—the bone-marrow—by varying agencies, than to an affection of a heterogeneous group of organs by a definite toxin.

Mere loss of blood is not sufficient to cause pernicious anæmia. After severe hæmorrhage the marrow becomes red in a few days, but the nucleated red cells found in the marrow and blood are normoblasts, and the effects of hæmorrhage where, presumably, the marrow is healthy are readily recovered from. We have never seen one acute or chronic hæmorrhagic anæmia develop into pernicious anæmia. Indeed in the histories of pernicious cases any reference to hæmorrhage is rare, and in our experience, even in the fully-established cases, bleeding is not nearly so common as is generally supposed, and, apart from hæmorrhage into the retina, is practically confined to the terminal stages and to the more acute cases.

On the other hand, blood destruction by such agents as phenylhydrazin, which has also toxic effects on the bone-marrow, is followed by megaloblastic as well as normoblastic blood formation.

Rosenqvist [1] has made an important study of metabolism in pernicious anæmia, and finds that there is a toxic increase in nitrogen metabolism.

The toxæmia is paroxysmal, owing to the production of a temporary relative immunity which in our view would account for the temporary improvements seen in the blood condition, indicating corresponding improvement in the bone-marrow.

We admit, of course, that hæmolysis may precede defective hæmatogenesis, but hæmolysis does not produce the various phenomena found in pernicious anæmia until the bone-marrow has undergone megaloblastic degeneration. The essence of the disease is not mere hæmolysis or poisoning of the circulating blood; it is a toxic affection of the bone-marrow.

Our subsequent experience has given us no reason to alter the views regarding the nature of pernicious anæmia which we published in 1904.[2]

1. The essential feature of the disease, and the criterion in its diagnosis, is that it is a megaloblastic anæmia.

2. The widespread evidences of blood destruction occurring in liver, spleen, hæmolymph glands and marrow indicate abnormal vulnerability in the blood-cells rather than a pathologically excessive hæmolytic action on the part of so many diverse tissues.

3. The accumulation of iron in the liver is due partly to the disintegration of weakened or weakly blood corpuscles by endothelial cells and leucocytes, and partly (and to a much greater extent) to storage of iron, which is the product of red blood corpuscles which have been disintegrated by phagocytes or toxins elsewhere. This accumulation of iron in the liver is not peculiar to pernicious anæmia, and is the natural result of the abnormal amount of blood destruction.

4. There is no direct evidence of special disease of the intestine, and the intestine need not be the primary seat of toxin production, though in certain cases, and notably in bothriocephalus anæmia, it is so.

5. In some part of the body a toxin is produced which acts directly on the bone-marrow, interfering with normoblastic blood formation, leading to megaloblastic formation, and acting with negative chemiotaxis upon leucocytes, especially of the neutrophil variety.

[1] *Zeitschr. f. klin. Med.*, Berlin, xlix. 1903, 193.
[2] *Journ. of Path. and Bact.*

6. The large red blood corpuscles produced by such a marrow, perhaps as much from their size as from inherent weakness, fall a ready prey to endothelial cells and leucocytes in the "hæmolytic" organs, notably hæmolymph glands, spleen, and marrow, and in the more acute cases the liver also.

7. It is quite possible that certain individuals from congenital defect in the marrow may be specially prone to the disease, as there is little doubt that the megaloblastic degeneration represents a reversion to the fœtal type. This applies specially to the hereditary or family type of the disease.

Symptoms.—The onset of the disease is always insidious. It is a remarkable fact that in practically all large collections of cases the blood count has been about 1,200,000 when the patient first came under observation.

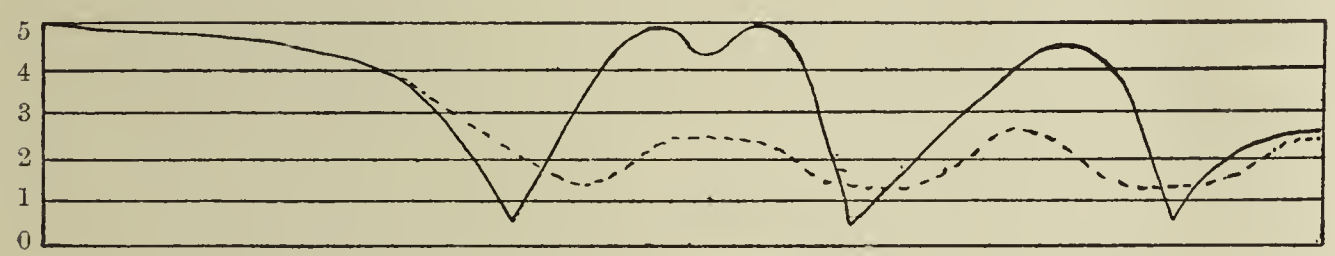


FIG. 23.—SCHEMATIC CURVES TO ILLUSTRATE THE ONSET AND COURSE OF ACUTE AND CHRONIC CASES.

(Continuous line, acute; broken line, chronic.)

The horizontal lines indicate the blood count in millions per c.mm. Note the insidious onset in both types, the much more rapid onset of relapses, and the comparatively brief period of the most serious phases. When the count is below one million, patients either soon die or have an early remission.

The patient practically always complains of muscular weakness. While this is the almost universal complaint that causes the patient to seek medical advice, the patient's strength in relation to his blood count is remarkable. In no other condition of anæmia with such low blood counts could patients do the amount of work that is sometimes done by sufferers from pernicious anæmia.

The peculiar lemon-yellow pallor, the breathlessness, the feeble pulse and the fever in a typical case present a picture which could hardly be mistaken.

On the other hand, a patient often comes complaining of weakness; the pallor may not be noticeable or noticed, other symptoms are vague or misleading or wanting, and the disease is very frequently overlooked, Patients almost always appear well nourished. There is no loss of subcutaneous fat, and there is often a slight

generalised œdema which helps to carry out the suggestion of plumpness.

Alimentary System.—There is almost always loss of appetite, in some cases even a repugnance for food. In a few cases, however, appetite remains good, and in still fewer cases it is excessive.

Hunter's suggestion that the disease is due to carious teeth and filthy mouths may be dismissed at once. We have seen many cases in people who had been edentulous for many years, and many others in people with mouths that had been well cared for. Even in hospital patients the mouths of pernicious anæmias will often compare favourably with those of their neighbours suffering from other diseases. In some cases sensitiveness and soreness of the tongue, hard palate, gums and cheeks have been noticed. Hyperæsthetic points may be noted and seem to correspond to submucous hæmorrhages. Shallow red ulcers of the tip and edge of the tongue are sometimes seen, and may serve to draw attention to a possible blood change. We saw recently a lady whom we had known for many years, who was habitually pale as the result of a cardiac lesion, and whose blood on several previous occasions had been found to be normal. She complained of a sore tongue of this type, and was found to have 3,600,000 reds; hæmoglobin, 82 per cent.; colour index, 1·1. She presented at the time no other typical symptoms, and recovered for a time under arsenic, but ultimately died in a second attack. These small ulcers may precede by a year or two any other definite symptoms, but where they exist we have always found that the blood already showed the typical change, though usually only in a minor degree. Diminution in the total red count, a colour index of 1 or a little over it, slight poikilocytosis, occasional polychromasia or basophilia, and a low leucocyte count will cause pernicious anæmia to be suspected in these cases.

Pigmentation of the buccal mucous membrane has been noticed, but is rare.

There is not infrequently a sensation of pain or discomfort in the epigastrium.

Attacks of vomiting occur in some cases at intervals, and are occasionally prolonged for weeks. No food at all may be retained, and rectal feeding may be required.

As a rule hydrochloric acid is absent after an Ewald's test-meal, or greatly diminished. We have only seen three cases, in which this point was investigated, in which the total acidity and proportion of free hydrochloric acid were normal, or even approached the normal. Attacks

of diarrhœa occur with great frequency, and are often associated with the attacks of sickness. Diarrhœa may be the main symptom, and we have seen cases in which the diagnosis of tubercular and malignant ulceration of the bowel, sprue, mucous colitis, etc., had been made before the blood was examined. The liver is not usually enlarged in acute or early cases. In chronic cases enlargement is not uncommon, but is seldom very great in amount. We have seen enlargement of the liver come and go with successive attacks and remissions.

The character of the fæces varies greatly. They may be quite normal to the naked eye and on microscopic examination, but in cases with gastro-intestinal symptoms may be of peculiar chrome colour, not unlike that of new brown boots, and may contain a good deal of mucus. In other cases of this type a fair amount of blood may be found by the benzidine and other reactions, or the stools may be pale and coated with mucus or muco-pus. Hæmorrhages from the bowel may occur.

Hæmopoietic System.—The spleen is always firm in consistency; its size is variable. In the great majority of cases it is not enlarged, but in a fair number of cases it may be slightly enlarged, and in a still smaller number of cases its enlargement may be considerable, but its lower border is very seldom more than about an inch below the costal margin. It follows the same rule as the liver as regards the time in the disease when enlargement is found. Cases with marked enlargement of liver and spleen have always lasted for a considerable time, and the prognosis is relatively though not absolutely bad.

The lymphatic glands are not demonstrably affected. The other ductless glands show no change.

Circulation.—Palpitation is frequently a distressing symptom. Dyspnœa is brought on by slight exertion. Faintness is not so frequently complained of, but we have seen cases in which there were repeated syncopal attacks. These may even be fatal. In severe cases the heart's action is excited; in other cases it may be difficult to localise the cardiac impulse either by inspection or palpation. The area of cardiac dulness is not usually abnormal, unless strain has produced dilatation, or there be some pre-existing cardiac lesion. A soft blowing systolic murmur can usually be heard over the different orifices in bad cases; in milder degrees murmurs may only be heard at certain areas, may be present intermittently or only after exercise, or not at all. They are much less frequently heard in elderly patients. Diastolic murmurs are rarely heard. Murmurs over the jugular veins are present in severe cases. The pulse is always increased in frequency. It is

generally over 80, even during remissions. With slight exercise it increases to 110 or 120. It is of small volume and low pressure, and the arterial wall is not specially thickened. Irregularity is seldom noticed unless there be some pre-existing cardiac condition with which this is associated.

Respiratory System.—There is little to note in the absence of complications. Many patients have a slight and sometimes an irritating persistent cough.

Integumentary System.—The pallor of the skin in a typical case is striking; it has a peculiar waxy lemon-yellow tint, which is practically diagnostic. This tint is, however, not always present, and it must be remembered that patients with a fairly high count of red cells may not show any noticeable pallor. For example, a patient with a count of 3,000,000 reds, and hæmoglobin 80 per cent., will have a practically normal complexion. The mere count may bear little relation to the pallor. For example, we saw a patient recently with a red count of 2,300,000, hæmoglobin 60 per cent., who showed the lemon-yellow tint remarkably well. At this time she was suffering from gastro-intestinal symptoms, with high fever. A month later these symptoms had disappeared under treatment, and though her red count and hæmoglobin were practically the same, her complexion was of good colour, with only very slight pallor. The toxæmia in acute cases, or cases with acute symptoms, has as much to do with the complexion as the anæmia. There is sometimes an ordinary untinted pallor, but there is seldom the deathly whiteness which is seen in chronic Bright's disease, or post-hæmorrhagic anæmia. Some patients have a somewhat brownish colouration, which is apt to obscure the real pallor, while weather-beaten faces may not suggest anæmia at all.

A quite definite icterus is seen in the skin and conjunctivæ, in a small proportion of cases. The lemon-yellow tint is due to a slight toxæmic jaundice in addition to pallor, and is only seen in cases which are not doing well or where toxic symptoms are marked.

Pigmentation resembling that of Addison's disease is not uncommon. It is more frequent in people who have taken much arsenic, but occurs also in untreated cases seen for the first time, and may confuse diagnosis. As regards position and character, it may exactly simulate the pigmentation of Addison's disease, or may be less typical. It is almost always most marked on the abdomen.

A slight persistent œdema of the lower eyelid and ankles is a common symptom, and the œdema may be more general.

Small petechial hæmorrhages are fairly common. Larger hæmorrhages are rare. Petechiæ may be seen in the mucous membrane of the mouth. Hæmorrhages are much more common from mucous membrane than from the skin.

The skin is dry, but slight exertion or excitement easily lead to profuse perspirations.

Genito-Urinary System.—The urine in all ordinary respects shows little abnormality. The specific gravity is usually low.

A marked "indican" reaction is usually obtained, and a colour reaction on the addition of nitric acid is common. These may be taken as evidence of absorption of products of putrefaction from the bowel and thus give useful indications for treatment.

Considerable importance has been attached to the occurrence in the urine of urobilin, but the probability is that urobilinuria is more or less an accidental occurrence at any time, and might happen in health just about as readily as in pernicious anæmia.

A transient albuminuria is not uncommon during the acuter stages of the disease, and association with acute, or more usually chronic, Bright's disease is not very rare. In our post-mortems we have been struck by the fact that the kidneys are practically never normal, and it is probable that the stupor and coma which often occur in the terminal stages are at least partly due to chronic uræmia. Many of these cases die with a relatively high red count, often over a million, while some of the cases with counts of 400,000 or so remain clear mentally until just before the end. We have seen cases terminate by ordinary acute uræmia, with convulsions, and sometimes complete suppression of urine. In the most marked of these last cases the patient was pregnant, and the suppression occurred as the result of premature labour.

Rosenqvist found a periodic increase of nitrogen. The output of phosphates is increased.

Menstruation nearly always ceases in established cases, but may return during remissions. We have recently met with several exceptions to this rule, all in women approaching the menopause. In two cases fibroid tumours of the uterus were found to be present. We were struck with the comparatively small lowering of the red cell count—or absence of change—in those cases as the result of what was sometimes pretty severe bleeding.

Nervous System.—There are nervous symptoms of some sort in about 30 per cent. of cases. In most instances these are subjective sensations of tingling or numbness in the feet and legs, more rarely or in less

degree in hands and arms. There is sometimes diminished sensibility and weakness, and less frequently there is actual neuritis. It is often difficult to determine to what extent this may be due to arsenic.

Cord symptoms sometimes occur. They are often indefinite, and as a rule are less than the lesions found after death might have been expected to occasion. The deep reflexes are frequently diminished or lost.

Symptoms of degeneration of the posterior columns, or of both posterior and lateral columns, are the most definite of all the nerve symptoms. These may go the length of marked ataxia, and may closely simulate tabes dorsalis. Spastic symptoms are much less common. The severity of the cord symptoms bears no necessary relation to the anæmia, and when once established they tend to be slowly progressive as a rule, though they may remain stationary. They usually begin during a period of anæmia, but not invariably, and persist even though the patient is otherwise well. We have seen a patient who was completely bedridden by his ataxia whose blood count was quite normal, though the film showed the changes we describe as occurring during remissions. He had a history, however, of two undoubted and severe attacks of pernicious anæmia some years previously. Sometimes the nerve symptoms are complained of before the symptoms of anæmia, and one may show exacerbations or amelioration without the other being affected. We have seen one case in which the cord symptoms began as spastic paraplegia with some rigidity, increased knee-jerks, clonuses and extensor response. Sensory symptoms, with the exception of tingling in legs, feet, and hands were absent. A few months later the signs of increased muscle tone had passed off, the knee-jerks could hardly be elicited, there was no plantar reflex of any kind, and there was definite loss of sensation in both legs. The anæmia in this case was of chronic type, and showed very little change throughout. The probability is that the degeneration does not depend on the anæmia so much as on a toxin which is the cause of both.

Mental Symptoms.—Patients, as a rule, do not exhibit that irritability of temper which is sometimes seen in other severe anæmias. On the contrary, there is commonly a great complacency, both as regards surroundings and as regards the gravity of the disease. Exceptions are, of course, met with, and the intelligent patient who takes too keen an interest in his temperature and the number of his red corpuscles may provide himself with a good deal of worry and his medical attendant with opportunity for the exercise of a considerable amount of tact.

Neurasthenia is not an uncommon symptom, and we have seen one case in which neurasthenia existed for years before the blood changes were present. The converse is, of course, much more frequent, and many an unfortunate patient with pernicious anæmia is labelled neurasthenia simply because the blood has not been examined.

Sleeplessness is often a distressing symptom. It sometimes, but by no means always, depends on gastro-intestinal disturbance, and disappears when this is successfully treated.

Actual mental symptoms are sometimes seen. Maniacal attacks, hallucinations, and delirium may occur, usually towards the end of the disease. In a small proportion of cases mental symptoms are very prominent. In one of our cases there was a history of an attack of anæmia twelve years before, followed by insanity, which necessitated detention in an asylum for nearly a year. She remained well for eleven years, and came into our hands with a second attack of pernicious anæmia. In the course of this she again became insane, and died suddenly while the arrangements for her removal to an asylum were being made. A fairly constant feature of the insanity of pernicious anæmias is its association with delusions of suspicion and persecution, and unfortunately it is usually near relatives who are suspected by patients. We have seen very distressing cases where husbands, wives, and favourite children were execrated by their spouses or parents. As with the cord symptoms, the mental symptoms may bear no relation to the anæmia. In one remarkable case a patient became insane without obvious anæmia, improved, and at last recovered mentally as pernicious anæmia became progressively severer, and again relapsed mentally as his blood returned to the normal.

Speech is sometimes slow and slurring, but often suggests that the patient will not take the trouble to articulate his words.

Special Senses.—Eye symptoms are common; subjective symptoms are sometimes complained of. There may be dimness of vision or flashes of light, there may be œdema of the lower eyelid, and there is sometimes hæmorrhage into the conjunctivæ.

Retinal hæmorrhages are common. The optic disc is very pale, so that the hæmorrhages show up with great distinctness. They may be small and punctate, or may occupy the whole disc. In one case a patient complaining of dimness of vision was found to have a double central scotoma, without change in the discs. His reds were 3,200,000, his hæmoglobin 80, the film very characteristic, but he did not look pale. He died of pneumonia about a fortnight after coming under observation.

Tinnitus is a common symptom. Deafness is rare, but may become very marked. It may be due, in some cases, to hæmorrhage into the inner ear, but this has not been demonstrated so definitely as in leukæmia.

Eichhorst has noted loss of smell and taste, and we have seen one case in which both senses were practically lost without local defect. Improvement in the anæmia was accompanied by improvement in both senses, but complete recovery did not occur.

Locomotor System.—The muscles are soft and flabby. Pain over the long bones is often present, and may be associated with tenderness. The pain is seldom mentioned without a leading question.

Temperature.—Fever is present at some time in about two-thirds of the cases; it is most uncertain in its incidence and duration. The temperature may be normal or subnormal for weeks or months and then it rises to 101° or 102°, and with a daily variation of about a degree remains high for weeks and then may as unaccountably subside. The fever is most commonly seen in acute cases, but apart from that observation it appears to bear little relation to the severity of the disease or to the blood changes. It is sometimes accounted for by intestinal, pulmonary, or septic complications, but often occurs without any cause which either ante- or post-mortem evidence reveals, and seems not infrequently to be due to the inability of the already overworked liver to deal with toxins.

The Blood Changes.—When a case comes under observation for either anæmic or gastro-intestinal symptoms the changes in the blood are usually already well marked and definite. An average estimation would be reds, 1,500,000.; hæmoglobin, 40 per cent.; colour index, therefore, 1·3; whites, 4000. These figures are, of course, subject to wide variations, for patients vary greatly in their sensitiveness to anæmia. Sometimes the figures are much higher — with a count of from 2,500,000 to 3,000,000 reds; sometimes the count will have dropped to 1,000,000. One reason for this difference is probably the rate at which the blood deterioration has progressed. If it has been gradual the lower figures are more likely to be reached; if it is rapid the upper are more likely to be observed. With a slow blood change the organs become accustomed to the anæmia; with a rapid fall in corpuscles diminished oxygenation is felt more quickly. The colour index also varies considerably at this stage. The more chronic the case the more likely is it to be 1·0 or just above 1·0, while in the acuter and more severe cases it may reach 1·5, and in isolated cases may go even higher.

The average is 1·2 or 1·3. The raised colour index is the most important single point in the diagnosis of pernicious anæmia. No other of the ordinary anæmias ever show a colour index above 1·0, although indices of 0·9 may be reached by very severe secondary anæmias of hæmorrhagic or septic type. The only condition of importance in which the colour index may sometimes be above 1·0 is acute lymphatic leukæmia, and in that case the blood changes in other directions are sufficiently characteristic to make the diagnosis easy. The cause of this raising of the colour index has been considerably debated. Some authors have gone the length of assuming that hæmoglobin must be present, dissolved in the serum, in order to produce it. But hæmoglobinuria is of very rare occurrence in pernicious anæmia, and it would of necessity be much more frequent were hæmoglobin to be anything like so constantly present in the serum as the constancy of the raised index would demand. The more reasonable explanation is that the red corpuscles on the average contain each a greater quantity of hæmoglobin than they should do, and that this is the reason is borne out by the facts that so many of the red corpuscles are larger than normal when examined in films, and also that it is often possible to diagnose pernicious anæmia when one is counting the red cells diluted with Hayem's solution, because of their deeper colour and larger size in the counting chamber.

The leucocytes are almost invariably diminished, the average number being somewhere about 4000, although in early favourable cases 6000 or 7000 may be found. Leucocytosis is exceedingly rare, and very seldom attains a high figure. The ordinary influences which produce this change do not appear to act in pernicious anæmia. For example, we have, on several occasions, seen a patient pass through, and recover from, an attack of pneumonia without the leucocytes being altered in any way, and on many occasions we have seen terminal septic conditions fail to raise the count. On eight occasions we have noted a leucocytosis. In six of these it did not rise above 15,000. In five of the cases there was albumin in the urine; in two, counts of 10,000 and 12,000 remained unexplained, and were quite temporary. In the last case there was a leucocytosis of 56,400. Reds were 2,470,000; hæmoglobin, 65; colour index, 1·3, with a very typical film. The urine contained albumin, and there was an acute left-sided pleurisy and pericarditis, with high temperature. The urine was suppressed soon after the patient was seen, and she died two days later. We have been specially struck by the association of kidney mischief with leucocytosis

in this disease, but there may be definite chronic Bright's disease with a subnormal white cell count. On the other hand, there may be extreme leucopenia. A recent instance will illustrate this. A lady of 70, who had been anæmic for about a year, suddenly developed a temperature of 103°, with a rigor and retention of urine. The physical signs when she was seen immediately after were not definite, but a pneumonia developed, and she died two days later. The count was—red cells, 1,570,000; hæmogoblin, 38; colour index, 1·2; whites, 1000. The film was typical as far as the red corpuscles were concerned, but all the white cells appeared to be lymphocytes, both in the counting chamber and in the films. This would naturally make one think of an acute lymphatic leukæmia, but the long history of anæmia, the characters of the blood in other respects, the absence of enlargement of liver, spleen, or lymph glands, made one consider that one was dealing with a very severe infection which was excluding from the blood the probably small number of polymorphs previously present. The subsequent development of a fatal pneumonia confirmed this view. Such cases are rare, however.

Examination of Film Preparations.—In making films the observer will generally notice that the blood spreads out much more easily than usual, and this is, of course, more marked the more anæmic the blood. Often when the blood is drawn it does not look homogeneous, but the corpuscles tend to separate themselves almost at once from the plasma, so that it looks like a badly-made emulsion of red particles in a pale yellow fluid.

The Red Corpuscles.—When compared with normal blood it will be seen at once that the average size of the corpuscles is larger in this disease, and if a film of normal blood and one of pernicious anæmia be stained at the same time and in exactly the same way, the corpuscles in the latter will be found to have taken on more of the stain. This statement, however, applies only to the average, for there are great variations in different cases in the actual appearance of the corpuscles. Sometimes they are almost all equal or nearly equal in size, sometimes very large ones are found side by side with very small ones, and the small ones may be so numerous as to bring down the colour index to unity. A recent case examined by a very competent observer nine months before we saw her had a colour index of 1·15 with all the red corpuscles large. Two estimations by ourselves at a fortnight's interval gave an index of just over 1 on both occasions. The large and small cells were about equal in numbers. Poikilocytosis may be very marked

or may be almost entirely absent, and the alteration in the shape of the corpuscles does not seem necessarily to be connected with any difference in the clinical course of the disease, although, as a rule, the chronic cases are those which show least poikilocytosis, the acute ones those which show most. As a rule the corpuscles in the former case show a rounded outline, but in certain cases large numbers of them are more or less elongated or oval. It depends very much on the spreading of the film whether the central concavity is well seen or not. In the thinner parts it is apt to disappear, while if a thick film be examined it

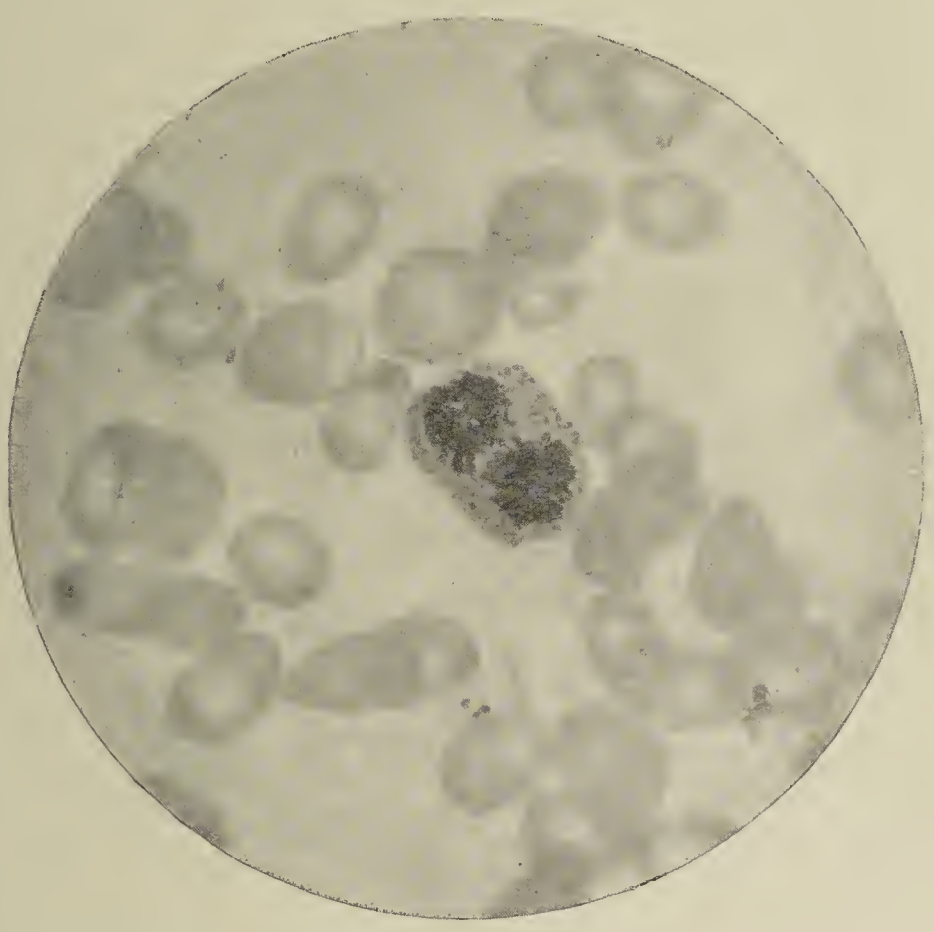


FIG. 24.—PHOTOGRAPH OF BLOOD-FILM FROM CASE OF PERNICIOUS ANÆMIA SHOWING A MEGALOBLAST IN MITOSIS.
Eosine and methylene blue. × 1000.

can often be found to be still present, and to have round it a much thicker, plumper rim of cell plasm than the normal corpuscle. A considerable proportion of the corpuscles are often found to show the cup shape. Polychromasia is very common. As a rule the large corpuscles or megalocytes are most liable to show it, but sometimes one finds the change pretty evenly distributed throughout the film, and again, if normal blood be stained along with a film from a case of pernicious anæmia, the red corpuscles in the latter may sometimes all exhibit a bluish tone as compared with the colour of the normal corpuscles. Granular degeneration, or basophilia, is seen more frequently in this disease than in any other, but varies very strikingly in its incidence in individual cases. Whole films taken from chronic cases may be gone

through without a single example being seen, while, on the other hand, acute cases may show the change in every tenth corpuscle, or even more often. Like polychromasia, the demonstration of basophilia depends very much on the way in which the film is stained, and it is therefore very important to treat the films from every case of pernicious anæmia in exactly the same way, to use a staining solution of uniform strength for a uniform time, and to make the time of washing out always the same. Prolonged staining and prolonged washing may destroy both of these appearances. Nucleated red corpuscles occur with very varying frequency. One can seldom reckon on finding them with anything like ease if the red count be above 2,500,000. If it is below that they are always to be discovered, although, in some of the chronic cases in particular, a prolonged search may be necessary, extending over perhaps even half a dozen films. They are almost always of the type known as megaloblasts. Normoblasts, in our experience, are rather rare in the pernicious anæmias of adults at any rate. In children they are more often to be found. The type of megaloblast varies very greatly. The cell is always large—from two to four times larger than an ordinary red corpuscle—and the cell body may stain in the ordinary way, but often shows a greater or less degree of polychromasia, or even basophilia. We have very often seen basophilia in cells dividing by mitosis. The nucleus may be large, occupying as much as half of the cell. In this case it is pale, and the intranuclear reticulum widely spaced. All variations in size and staining may be seen between this form, which may be regarded as typical, and a small pyknotic deeply-stained homogeneous nucleus usually situated towards one edge of the corpuscle. Forms with a rounded nucleus occupying a little less than one-third of the diameter of the cell are very common. It is by no means infrequent, especially in acute cases, to see cells in the various stages of mitosis, but it is still more usual to find the nucleus broken up into two, three, four, or more parts, connected with one another by strands of chromatin, or sometimes separate—the so-called karyorrhexis, a degenerative change. Some authors go the length of refusing to diagnose pernicious anæmia in any case in which megaloblasts cannot be found, and it is certainly wise to search for them diligently, yet hardly necessary to examine a dozen films minutely in the hope of finding them in chronic cases with the colour index just above 1. They are almost always to be found with much greater ease when patients are going about, or within the first day of their stay in bed. Thereafter they may entirely disappear from the blood of even very severe cases. Generally

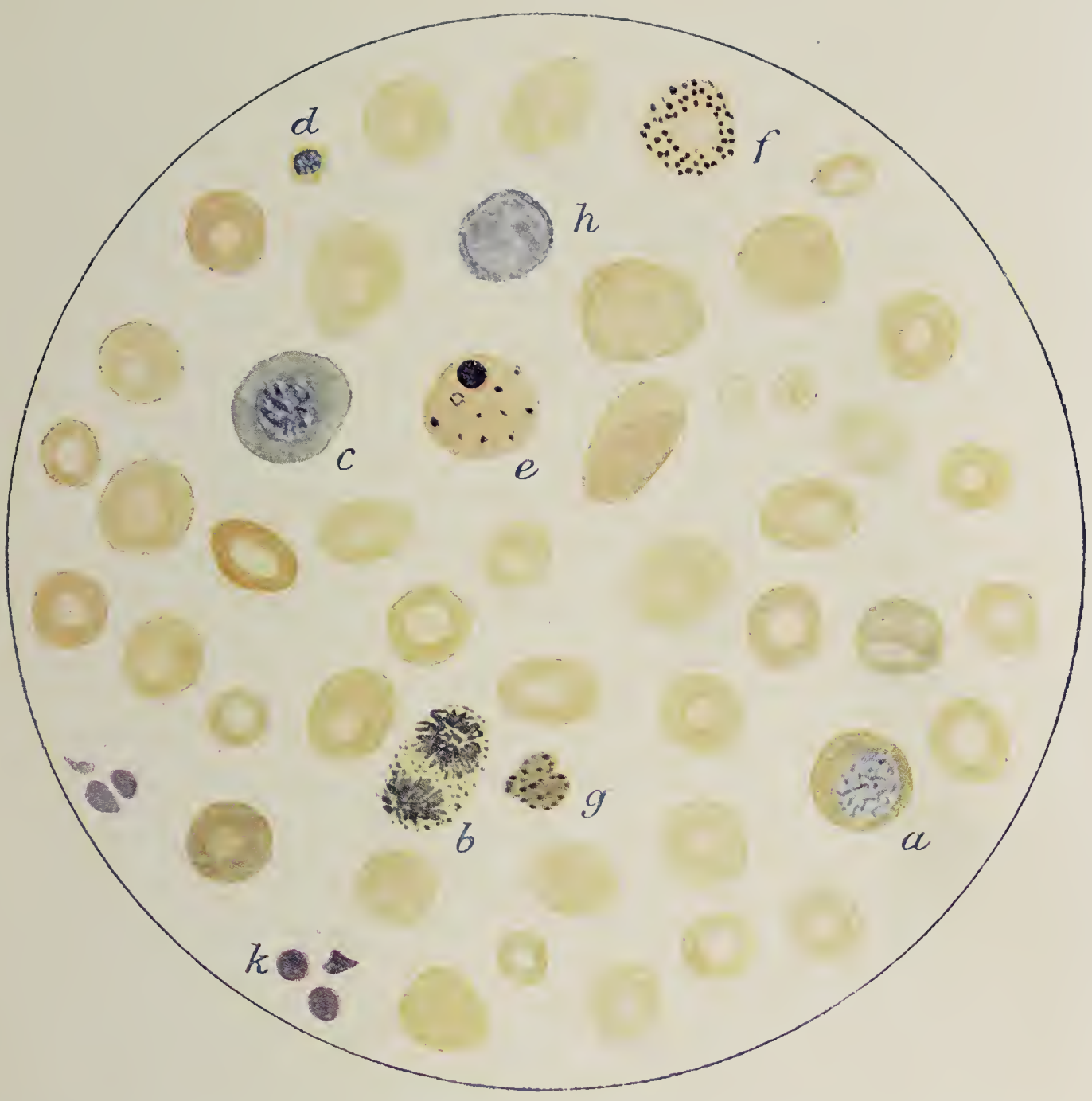


PLATE VII.—BLOOD FILM FROM CASE OF PERNICIOUS ANÆMIA (Jenner's Stain).

The average size of the red corpuscles is increased. Megaloblasts (*a*, *b*, *c*) are present.
(*a*) Typical.
(*b*) Showing mitosis and punctate basophilia.
(*c*) Showing very marked polychromasia.
(*d*) A microblast.
(*e*) A pyknotic normoblast with a "Cabot's ring" and granular basophilia.
(*f*) Erythrocyte with punctate basophilia.
(*g*) Erythrocyte with polychromasia and punctate basophilia.
(*h*) Lymphocyte.
(*k*) Collection of blood-plates; note large size.

A. G., *fecit*.

speaking, one finds post-mortem that the cases which showed a large number of megaloblasts in the blood during life show a large number in the marrow. While the rule holds good that cases with a low red count are more likely to have many megaloblasts, this is by no means invariably true. We examined recently the blood of a patient with a red count of 600,000, in which an occasional megaloblast could only be found after much search.

Some megaloblasts are found of extraordinary size. These are known as gigantoblasts, and are usually said to indicate a bad prognosis. We have, however, seen cases recover whose blood contained them. They generally possess a large open nucleus. Microblasts are found in some cases. Their origin is not definitely understood; they generally look like degenerated megaloblasts or normoblasts. The nucleus is small, sometimes stains deeply, sometimes hardly at all, and the cell body, instead of possessing the firm-looking rounded contour of the other blasts, is usually irregular and jagged, and shows marked polychromasia. They are seldom found unless a large number of megaloblasts are to be seen, and do not seem to possess any special significance, except as nucleated red cells.

The Leucocytes.—As might be expected with the usual low count, there is generally a polymorph leucopenia or relatively high lymphocyte proportion. Such a proportion as polymorphs 40, lymphocytes 60, is very common. A high proportion of the lymphocytes are of the small variety; sometimes no larger ones can be found. Eosinophils are often seen in about the normal proportions. It has been stated that their presence gives a good element to prognosis, but we have not been able to confirm this. Basophils are rare. In severe cases, and sometimes just before death, neutrophil myelocytes may appear in small number. The polymorphs are often large and oval, with a nucleus broken up into 5, 6 or more lobes.

The Blood-Plates.—These are invariably diminished in severe cases, and sometimes seem almost to disappear. We had noticed that in some cases the plates were much larger than usual, nearly half the size of a red corpuscle, and found, in conversation with Dr. Cabot, that he had made the same observation. The reason of this is not apparent, but so far as it goes it tends to support the view that blood-plates are representatives of the nuclei of red corpuscles. As cases improve, the plates become more numerous, and sometimes during recovery, and especially at the stage of low colour index, may be as numerous as in a secondary anæmia.

Staining of Blood-Plasma.—In severe cases it is sometimes found

if Jenner's stain be used for a short time and washed out rapidly that the dried plasma between the corpuscles takes on a light blue stain, with a clear space round the corpuscles. This is sometimes seen also with severe secondary anæmias, but never so well marked.

Alterations in the Blood during the Progress of the Disease.—In a case which is going downhill the behaviour of the blood will vary a good deal according to the previous acuteness or chronicity of the case. In the acute cases the tendency is for the corpuscles to diminish steadily in number and for the colour index to rise, or at any rate remain high. More and more megaloblasts may appear, and these are often at their maximum just before death, because of the agonal disturbance of the circulation. They may be found also in large numbers if the blood taken from the heart at a post-mortem examination be examined. The red count with which patients die varies very considerably. It may not have fallen below 1,000,000, and in these cases patients probably die from some other cause than the anæmia. In other cases it runs down to much lower figures. We have only once seen a case recover where the red count had fallen as low as 400,000, but that patient, after being practically comatose for nearly a fortnight, picked up and had a remission for nearly eighteen months. Quincke's count of 143,000 has never been equalled. The patient in that case recovered. On the other hand, in the chronic cases the count almost never falls below 1,000,000, and megaloblasts are often very scanty indeed even as death approaches. The leucocytes usually remain at about the same figure throughout, generally with a slight tendency to fall towards the end. We have very seldom seen an agonal leucocytosis.

In cases which are going to recover, the red corpuscles sometimes increase with startling rapidity. There may be a rise of 1,000,000 a week, although that is exceptional. The colour index, if it has been high when the patient was at the lowest ebb, gradually drops. If, for example, it has been 1·4, at the end of ten days it may be 1·3, and after similar intervals 1·2 and 1·1. The corpuscles themselves look more natural, basophilia and polychromasia become less marked, and megaloblasts disappear. A certain number of cases never reach a completely normal blood, and seem incapable of getting beyond about 3,000,000 reds, with hæmoglobin of 65 or 70 per cent. These, as a rule, have but a short period of comparative health and soon drop back again, but a certain number drift into the chronic form, and may last in that way for a long time. Cases occasionally show marked improvement in symptoms under treatment, with little or no real

improvement in the blood. We may quote the case of a man, aged 42, who had great weakness, dilatation of the heart, œdema of the legs, constipation and dyspepsia. Red corpuscles 1,650,000, hæmoglobin 40, colour index 1·2, leucocytes 3800, a fair number of megaloblasts. In three months the whole of the alimentary and toxic symptoms had disappeared. The heart was no longer dilated, and the œdema had gone. Red cells 1,700,000, hæmoglobin 45, colour index 1·3, leucocytes 4000. Megaloblasts had disappeared. Other cases reach a perfectly normal count in every way, and generally do so by passing through a period of relatively low colour index. A typical case of this sort might have the following counts at successive examinations :—

Reds.	Hæmoglobin.	Colour Index.
1,500,000	40	1·3
2,500,000	60	1·2
3,500,000	75	1·07
4,000,000	80	1·0
4,500,000	82	0·9
5,000,000	85	0·85
5,000,000	100	1·0

We have seen the colour index drop as low as 0·7, and it sometimes remains below unity for weeks. This is to be hailed as an excellent omen, for such cases generally have a long remission—if they are careful. But though the count may be satisfactory, the film usually shows some departure from the normal. There is generally a greater amount of inequality in size among the corpuscles than in normal blood; a few megalocytes will be seen, and careful search will generally find some polychromatic corpuscles or some punctate basophilia. We have occasionally found a stray megaloblast in cases with a practically normal count. During remission the leucocytes seldom stand at the normal figure of 7000. They may remain about 4000, or rise to 5000 or 6000—the higher the better from the point of view of prognosis.

It is very difficult to get a large mass of statistics regarding the behaviour of the blood as patients begin to go downhill. We find that neither patients nor doctors will take the trouble to have regular examinations of the blood made during the period of remission, and, just as at the commencement of the disease, patients do not usually come under observation again until the condition is well established. We have been able, however, to follow a few cases throughout, and have found in these that the process of declension is a gradual one. The red corpuscles drop slowly and the hæmoglobin rises relatively. The process can sometimes be arrested by treatment, and in cases

which do not respond it is sometimes found that there is an attempt from time to time at recovery which is not sustained.

Diagnosis.—From what has been said already, it will be evident that this always depends on the complete examination of the blood, and that there is no certainty to be attained unless this is properly done. The number of cases which present the classical clinical appearances does not reach a half of the total number, and it is wasting precious time to wait until they do so, if indeed they ever would do so. The disease is vastly more common than is generally supposed, and seems to be becoming more frequent. This statement is based, not on the obvious cases, which naturally find their way to professed hæmatologists, but on the number of cases found by systematic examination of the blood, whose condition does not suggest, or suggests only to the practised eye, the possiblity of anæmia, and who may appear to be suffering from the most various conditions. What will be said under the heading of "Complications" is of importance in this connection. The blood should be examined in every case which presents persistent and unexplained gastric or intestinal disturbance, especially if there be vomiting, diarrhœa, or sore tongue. Atypical chronic nervous symptoms of any kind, but especially if they are associated with the sensory apparatus, the peripheral nerves or posterior columns of the cord, unexplained debility, temperature, or dyspnœa should indicate a blood examination. The point is that the disease is easily missed if one is not on the lookout.

In cases which are definitely anæmic the same rule holds—examine the blood fully. High colour index and the presence of megaloblasts are the principal criteria, and leucopenia is a definite help. No clinical phenomena can be relied on with certainty. For example, certain cases of gastric cancer, with the tumour in an inaccessible position, simulate pernicious anæmia with almost absolute fidelity. The colour of the skin, the gastric disturbance and vomiting, the weakness and dyspnœa, the absence of free hydrochloric acid after a test-meal, systolic murmurs in the heart, are common to both, and we have often left a patient's bedside satisfied that we had to deal with one or other of these conditions, until the blood examination convinced us of error. Chlorosis is not worth discussing. The colour index is always so low that a mistake is hardly possible. It is different, however, with the severe secondary anæmias due to septic infection, hæmorrhage, or concealed malignant disease. In the great majority of cases, of course, the history and clinical phenomena point the way, but where these are doubtful

there may be a temporary hesitation. The reason for this is that, as pointed out in discussing the secondary anæmias, the lower the blood runs down the higher the colour index tends to become, and the more large red corpuscles appear in the blood. The megaloblastic reserve is more drawn upon and the megaloblasts turn out megalocytes into the circulation instead of dividing to form normoblasts. The index in these secondary cases never, in our experience, reaches unity, however, but tends to be about 0·7, or at the highest 0·9, and in the enormous majority of these cases there is leucocytosis. The difficulty is most common in cases of anæmia in the puerperium and in septic endocarditis without any obvious primary cause. As regards the first, practitioners are, naturally enough, most unwilling to admit the possibility of sepsis, and the well-known fact that pernicious anæmia does occur in puerperal women is used to cover a multitude of discrepancies in the blood examination. In both these diseases the anæmia may be very rapid in its onset—more rapid than in any pernicious anæmia. We have indeed seen septicæmias whose red cells had dropped from, presumably, the normal figure to 2,500,000 in three days. When nucleated reds are present, as they often are, they are either exclusively normoblasts, or towards the end of the disease a few megaloblasts may appear. Leucocytosis, with a high polymorph percentage and a well-marked glycogen reaction, is practically constant except in the intense fulminating cases which are so rapidly fatal that the suspicion of pernicious anæmia does not arise.

A word of warning must be said, however, with regard to colour index. Figures are dangerous things unless they are correct. We have found that mistakes are more frequently made in estimating hæmoglobin than in counting reds, and we would protest against the use of Tallqvist's hæmoglobin scale in the diagnosis of pernicious anæmia, unless it is checked by a more accurate hæmoglobinometer. It almost always reads too high, and the tendency of the inexperienced is to make it read higher still—we have seen readings by youthful enthusiasts 20 and 30 per cent. too high. Less than this might convert a colour index of 0·7 into one above unity. Some people have a congenital inability to match colours, and these persons are specially liable to make errors with the paper scale. They should always use one of the liquid methods in which transmitted light is used, for slight differences in shade are then much more obvious than they are with the opaque methods.

A difficulty of another kind sometimes occurs with leukæmias which

have reached the stage of marked anæmia. As noted elsewhere, the colour index may then rise to unity or just below it, and if, for some reason, such as a febrile complication or X-ray treatment, the number of leucocytes falls to normal or below it, the diagnosis might be in doubt if the case were seen for the first time. But, generally speaking, though the number of leucocytes falls, the proportions remain abnormal, and the abnormal cells present would help in the diagnosis. The ordinary clinical appearances in the case would also be helpful.

Sometimes practitioners send one films with the request for a diagnosis of pernicious anæmia or otherwise. In some cases it is quite easy to give an opinion, especially if many megaloblasts be present, in others quite impossible if these cells are absent and if the colour index be just about unity. A hæmoglobin estimation made at the same time is a great help, if it is reasonably accurate, for in practically all other chronic anæmias the reds are small and poorly shaped, so that an apparently normal film, with a low hæmoglobin value, should always arouse the suspicion of pernicious anæmia.

But, of course, in every case where it is at all possible, the diagnosis should be based on a complete blood examination.

Complications.—While the disease as such has few complications, it is often complicated in the most various ways. This statement applies perhaps especially to the cases occurring in later life, when the ordinary wear and tear has begun to tell on other organs besides the blood-forming ones. Here the anæmia is apt to be of a chronic type, and the additional or pre-existing disease bulks much more largely in the eyes of both doctor and patient. Thus we have seen association with various forms of cardiac valvular disease, with angina pectoris, with the Stokes-Adams syndrome, with arteriosclerosis; with various cancers, as of the larynx in one case, of the stomach in one case, with slow-growing scirrhus of the breast in two cases; with Bright's disease frequently, though, as we have remarked, it is a question whether the kidney mischief should not be regarded as part of the syndrome of pernicious anæmia; with renal and hepatic calculi; with cystitis very often, and, of course, with prostatic enlargement and its results in old men. We have seen it follow upon both exophthalmic goitre and myxœdema; and we might indeed enlarge the list indefinitely; for there are few of the ills that flesh is heir to which may not be interpolated into the course of the disease, or precede or follow it. We have never seen it associated with active tubercle, nor, judging from our post-mortem

experience, does it seem to have much association with healed tubercle. Many cases are cut short by pneumonia, influenza and septic complications. Terminal coma is common and is sometimes uræmic.

Duration and Course—Prognosis.—It is most important to take into consideration the cause of the disease. If the cause can be discovered and removed the outlook is good; if not, the disease will sooner or later be fatal. The cases due to bothriocephalus latus are the most satisfactory in this respect. The cases, too, which begin during pregnancy or the puerperium are likely to recover in at least a good many cases if the period of acute symptoms can be safely tided over. The serious element in these cases is the acute onset.

In the cases in which no cause can be discovered the course varies immensely. It is difficult to say how short the duration of life may be, since patients are practically always seriously ill before they are seen, but the fatal ending has come in fourteen days after the patient has first been examined.

It must not be taken that the immediate outlook is hopeless. We have had patients under observation for over twelve years, and cases of seventeen and twenty years' duration are on record.

One of the remarkable features of the disease is the occurrence of remissions. They sometimes begin quite abruptly in spite of severe symptoms, the red corpuscles increase at the rate of 200,000 per day, and in a few weeks a patient, apparently at death's door, appears in good health, and a month or two later a glowing account of the efficacy of the last therapeutic measure employed is published by a complacent editor.

Remissions may last for months or even for years. A patient may undergo as many as half a dozen remissions and relapses. During the remissions the chief characteristics of the blood may disappear, but in a majority of cases there is at least an element of suspicion in the appearance of films, even though the red cell count may closely approximate the normal 5,000,000. In many cases the remission is incomplete. Patients recover so far, and may then lead a life of semi-invalidism for some years.

In cases that are going to do well there is often a loss of weight in the first fortnight of treatment, due to the disappearance of œdema. The disappearance of the lemon-yellow tint, the cessation of gastro-intestinal disturbance, fall of temperature to normal, are all favourable symptoms.

In progressive cases there is a general decline in health and strength. Pallor, œdema, and weakness increase. The patient becomes first unwilling and then unable to leave his bed. Cardiac excitement is brought about by slight disturbance. Attacks of gastro-intestinal irritation may add to the patient's misery. Sometimes these symptoms develop with startling rapidity. They may be accompanied by jaundice, and the patient seems to be overwhelmed by an intense toxæmia. In other cases there is increasing weakness, some cachexia, apathy, and indifference, followed by coma and death.

In a disease with such diverse possibilities it is important to be able to try to form some opinion as to the probable immediate outcome of the disease.

The age of the patient or the incidence of such symptoms as sickness or diarrhœa, increase of the yellow tint or œdema, does not necessarily affect the ultimate course of the disease.

Febrile attacks add to the seriousness of the condition while they last. The patient may not be any the worse, and is sometimes better after they are over.

Hæmorrhages are a serious sign. It has been suggested that the retinal hæmorrhages are not so serious prognostically as the others.

The examination of the blood, and particularly the *repeated* examination of the blood, may give important information. Thus a case whose corpuscles are well under 1,000,000—say 800,000—rarely continues long at that stage. If the corpuscles have shown a distinct tendency to fall in about a fortnight, we may predict a fairly early termination.

On the other hand, if the tendency of the corpuscles is to rise, we generally find that our case will fall into one of two groups:—

(*a*) If the symptoms are well marked, we may expect a fairly satisfactory remission.

(*b*) If symptoms are not marked—dyspnœa, yellow colour, and fever absent or slight—the case will probably run a somewhat chronic course. The corpuscles will reach to between one and two million or higher, and remain at that point, it may be, for years.

When the blood changes are considered along with symptoms we find that most cases will fall into one or other of the following groups:—

I. Acute Favourable Cases

1. The symptoms are marked.
2. Red cells are much diminished, but show a tendency to rise.

3. Megaloblasts are atypical and not numerous.
4. Normoblasts are relatively numerous.
5. The colour index is high but tends to fall.
6. Polychromatophilia is not marked.
7. The percentage of polymorphonuclear cells is high, and the white count is not greatly diminished.
8. Myelocytes are absent or scanty.

Course.—A remission to a fairly normal condition, which may be maintained for years.

II. Acute Unfavourable Cases

1. Symptoms are marked, and there may be hæmorrhages.
2. Red cells are about one million, and tend to remain or go lower.
3. Megaloblasts are typical and numerous.
4. Normoblasts are less numerous than megaloblasts, or are absent.
5. The colour index is high.
6. Polychromatophilia is marked.
7. Percentage of lymphocytes is high and there is marked leucopenia.
8. Myelocytes may be numerous.

Course.—A fatal termination in from one to three months.

III. Subacute Cases

1. Symptoms are fairly well marked.
2. Red cells about one million, showing considerable variations in successive counts.
3. Megaloblasts are fairly numerous.
4. Normoblasts are scanty.
5. The colour index is high.
6. Polychromatophilia is distinct.
7. The percentage of lymphocytes is high in the absence of fever.
8. Myelocytes are fairly numerous.

Course.—The average duration is about two years, but complications may cut it short.

IV. Chronic Cases

1. Symptoms are not well marked.
2. Red cells tend to remain about one and a half or two million.

3. Megaloblasts are absent or scanty.
4. Normoblasts are seldom seen.
5. The colour index is generally about 1.
6. Polychromatophilia is slight.
7. The percentage of lymphocytes is high.
8. Myelocytes are scanty or absent.

Course.—Apt to be chronic. Patients can often work though they feel weak; and though febrile attacks, etc., may occur, they have little bad effect. Symptoms of nerve degeneration are not uncommon, but their incidence does not affect prognosis. Improvement seldom occurs, but the duration may be for several years.

Treatment. — The first essential when the diagnosis has been definitely made is to approach the treatment in a hopeful spirit, and not to allow oneself, or the patient, to be depressed by the adjective in the name of the disease. Too often the diagnosis is followed by the perfunctory prescription of arsenic and iron, with very little else in the way of treatment, and the gradual sinking of the patient is regarded as the natural course of the disease rather than as being due to want of treatment. As a matter of fact, there are few diseases of so serious a character for which so much can be done by careful and discriminating therapeutics. A large number of first attacks will get well with almost any treatment if the patients are placed under proper hygienic conditions, but the difficulty of recovery increases steadily in most cases, in geometrical rather than in arithmetical progression, with each successive attack. This does not apply, of course, to the very chronic cases, where the patients live for years in a state of semi-invalidism without any acute symptoms, and in which the blood never can be got up to the normal.

It is never wise to tell patients that they are suffering from "pernicious" anæmia, but they must be informed of the gravity of the condition, in order that they may intelligently second their doctor's efforts.

Rest.—Rest is of great importance for many reasons. Almost every case when first seen is suffering more or less from chronic cardiac strain or dilatation, even if the typical fatty change be not present, and if that is allowed to continue the blood will not improve. The digestion improves with rest; the generalised œdema, which is so common, often disappears with rest alone, and if the patient can be spared the worries of business and the importunities of anxious friends improvement is

more likely. Hospital for the poor and conditions as nearly as possible approaching those of hospital for the well-to-do are of great value. Sunshine and fresh air are potent factors. Patients should be open-aired as freely as phthisis cases in fine weather, but they must be carefully guarded from damp, cold, and chill. Bed should be insisted on until the hæmoglobin reaches 60 per cent. in the acuter cases. In the more chronic cases this need not be so rigorously enforced. As the patient recovers exercise may be gradually allowed, but its effect on the heart and pulse must be carefully watched. Even after complete recovery patients must be warned that they must take life more easily than before, both as regards work and play. In many cases recurrences are directly traceable to specially strenuous or long-sustained bodily or mental strain. We find that the disease is apt to attack energetic men, who in the joy of recovered health are prone to attempt to make up arrears of work, and so relapse, unless they are specially warned of the danger of overwork. In one case relapse seemed to be directly due to a long run to catch a train.

Diet.—Diet is almost equally important. In every acute or subacute case, no matter whether there be digestive symptoms or not, the diet should be restricted for a time to milk and farinaceous foods. Fish, meat, poultry, game, meat soups, extracts or juices must be rigidly tabooed. One often finds that the mere exclusion of these from the diet begins improvement. The reason for this is probably complex—the anacidity of the gastric contents, the imperfect intestinal digestion, with the tendency to decomposition of the contents of the bowel, the demands made on the already overburdened liver by the heavier nitrogenous foods, and the temporary or permanent alterations in the kidneys which we have shown are so constantly present, and which are probably due to the excretion of toxins, are all probably factors in demanding a simple and unirritating diet. The details of the *menu* must vary with the individual case. Patients with sickness and diarrhœa may require the severely simple régime of peptonised milk alone, and may gradually pass through the usual succession of Benger, milk puddings, bread and butter, eggs, etc. Cases with constipation often benefit by the addition of vegetables, stewed fruit, and fruit juices, provided these are not so acid as to upset digestion. Of course patients tire of a farinaceous diet, and the length of time during which it must be persisted with varies greatly. It should always be retained as the staple, even after return to health, but a certain amount of the more digestible meats may be allowed as improvement takes place. In patients with the "lemon-

yellow" tint of complexion the disappearance of this colour, which is evidence of a mild toxic hepatitis, may indicate some relaxation in diet, if the gastro-intestinal symptoms in other respects are improving. A good amount of fluid should usually be allowed unless there be great œdema. Weak tea and coffee do not seem to be harmful, but alcohol should be reserved for those cases and emergencies which require it.

Oral Antiseptics.—In a disease in which gastric disturbance is so common and so trying a symptom, it is obvious that septic conditions of the mouth, teeth, and pharynx should always be carefully treated whether one believes that they have anything to do with its causation or not.

Intestinal Antiseptics.—Intestinal antiseptics are often extremely serviceable as adjuvants. Our experience has been that a combination of small doses of calomel with salol, given in fairly large doses, is most useful; but all the intestinal antiseptics, and especially β-naphthol, have been tried, and are of service.

In cases with gastro-intestinal symptoms, moreover, we find that excellent results are often obtained by washing out the bowel with physiological saline, the amount being steadily increased as the lower bowel is cleared out. The value of this measure is as great in cases with diarrhœa as in those with constipation, and it is usually rapidly followed by disappearance of the lemon-yellow colour and by return of appetite. We make it a routine in all cases when they first come under observation. The constipation which occurs in some cases seems to be atonic from muscular anæmia. Occasionally, in cases with severe vomiting, we have washed out the stomach as well; but generally the patients are too weak to bear this, and it puts too great a strain on the heart.

B. Coli Vaccines.—Some cases have been treated with B. coli vaccines prepared from the patient's fæces, and we have heard of cases in which good results have been claimed. In our hands the measure has not been successful.

Arsenic.—As regards special medicines, arsenic is our sheet-anchor. It appears to act mainly by stimulating the normoblastic function of the bone-marrow, but perhaps also by virtue of its antiseptic or anti-toxic action. It is best given in solution, either as Fowler's solution or, perhaps better, as the hydrochloric solution, which is usually better borne by the stomach. It may be necessary sometimes to precede arsenic by a course of gastric sedatives. The dose is to be regulated by

individual tolerance, and, generally speaking, the larger the dose which can be taken the better the prognosis. The initial dose is to be decided by the digestive condition, and may be 1 ♏ or 4 ♏, according to circumstances, thrice daily after food, and well diluted with water. The initial dose, say 4 ♏, should be given for three days, then a minim added, this again for three days, and so on until the usual symptoms of slight overdose begin to show themselves. The arsenic should then be stopped altogether for two or three days until the symptoms have passed off, and then recommenced with a dose two-thirds the size of that reached, and continued at that level. Thus if 12 ♏ cause symptoms, the permanent dose should be 8 ♏. Of course other fluid arsenical preparations may be given, or the solid form may be used, but it is not so easy with this to graduate the dosage. Occasionally patients who cannot tolerate arsenic by the mouth can take it intramuscularly, as Fowler's solution well diluted. A single daily dose is generally given. Some patients show curious idiosyncrasies in their behaviour to arsenic. It may be well borne for a time, and then persistently upset digestion in spite of all that can be done to aid it by stomachics, etc. Or the reverse may occur. Or a patient who recovered smoothly from a first attack under arsenic may be quite unable to take it in a second. In some severe cases the attempt to push arsenic in any form may bring on rise of temperature, with or without gastric disturbance. Arsenic should never be continued after the red count has reached the normal figure.

The desire to give arsenic in large doses in this disease without the unpleasant effects which the inorganic preparations produce has led to the employment of all the organic preparations in turn; cacodylate of soda, atoxyl, soamin, arsacetin, and the rest have all been tried, and we experimented largely with them at one time. We were not satisfied, however, that the cases in which we got improvement did any better than they would have done with ordinary arsenic, and we found all of them in turn give rise to much more serious symptoms in certain cases than ordinary arsenic given in the usual way. For example, with atoxyl we have had two cases of very severe herpes, a well-marked arsenical neuritis, and in one case an intense febrile reaction with sickness, vomiting, and diarrhœa, which lasted for several days, and which recurred when a quarter of the original dose was again tried. In short, we were so dissatisfied with all these preparations that we ceased to give any of them, and fell back on the older method.

Salvarsan.—Since Byrom Bramwell introduced the use of salvarsan in the treatment of pernicious anæmia a large number of cases have been reported. In a recent paper Bramwell[1] records eleven cases. Of these four improved to a condition of health, two showed marked improvement, one showed slight improvement, two did not improve, and two died.

Salvarsan was injected intramuscularly.

Another recent series of eleven cases is reported by Boggs.[2] Two were practically moribund before the treatment and died; the remaining nine cases all improved.

Such favourable results are by no means universal, and numerous cases have been published in which salvarsan failed to benefit. Our own experience is not encouraging. In the following tables we give a note of our results in twenty cases.

The salvarsan was in each case given intravenously. The dose in most instances was 0·6 grm. In one or two cases the dose was smaller, and in several of the cases the injections were repeated more than once.

The neo-salvarsan in the cases quoted was given intramuscularly. The dose was 0·6 grm. in the non-chronic cases, 0·3 grm. in the severer ones, and in four instances the dose was repeated several times.

SALVARSAN

	Sex.	Age.	Duration.	Red Corpuscles in millions.	Hæmoglobin per cent.	Result.	Red Corpuscles after Treatment.
1.	M.	53	4 years	2·2	50	Improved	4·3
2.	M.	37	15 months	2·0	58	*In statu quo*	1·4
3.	M.	28	1 year	2·0	40	Died	0·3
4.	M.	59	9 months	1·3	30	Died	1·2
5.	F.	33	6 years	1·7	38	Improved	3·3
6.	M.	50	8 months	2·4	60	*In statu quo*	1·8
7.	M.	68	4 months	2·2	50	*In statu quo*	2·3
8.	F.	52	3 months	1·6	38	Improved	4·3
9.	M.	27	1 year	1·5	35	Died	1·0
10.	M.	50	2 years	1·6	40	Died	1·5
11.	M.	55	3 months	1·3	28	Died	0·9
12.	F.	61	3 years	2·6	60	Died	1·5
13.	M.	50	2 years	1·3	28	Died	1·0

[1] *Brit. Med. Journ.*, 24th May 1913.

[2] *Johns Hopkins Med. Bullet.*, October 1913.

Neo-Salvarsan

	Sex.	Age.	Duration.	Red Corpuscles in millions.	Hæmoglobin per cent.	Result.	Red Corpuscles after Treatment.
1.	M.	44	18 months	1·3	31	*In statu quo*	1·0
2.	F.	56	4 years	2·8	54	Died	2·7
3.	F.	48	6 months	2·0	30	Improved	3·9
4.	M.	56	3 years	2·8	60	*In statu quo*	2·5
5.	M.	48	8 months	1·5	40	Died	0·9
6.	F.	40	2 years	2·1	45	Died	1·7
7.	M.	43	6 months	1·2	33	Died	1·0

Summary

	Improved.	*In statu quo.*	Died.	Total.
Salvarsan . .	3	3	7	13
Neo-Salvarsan .	1	2	4	7
	4	5	11	20

In view of these results (and we have no knowledge of the duration of the "improvement" recorded), it is not surprising that our impression of this treatment is not favourable.

We have come to the conclusion that neither salvarsan nor neo-salvarsan should be given intravenously in acute cases.

The injection is followed by a reaction which affects the temperature and the heart and causes gastro-intestinal disturbance, which may persist for days. We have little doubt that in some of the very acute cases in our earlier experience of the drug the fatal issue was hastened by its use. In more recent times we have frequently refused to sanction the use of salvarsan in cases of this sort in spite of the importunity of the patient's relatives and the doctor in charge.

In subacute and chronic cases we are satisfied that no better results follow the use of salvarsan than ordinary arsenic. One of us recently had a striking illustration of this in hospital practice. Two cases of the same age, with similar blood-counts, and in apparently much the same physical condition, were admitted within a week of each other. One case received five intramuscular injections of neo-salvarsan, and was afterwards rather worse than better. The other case, treated with Fowler's solution, improved steadily, and went out with a normal blood-count and in good health. Both were first attacks.

After an intravenous injection of either salvarsan or neo-salvarsan a reaction is to be expected even when small doses have been employed. After an intramuscular injection, while the reaction is much less or absent, local pain may be very severe. This pain may be all the greater because of the enfeebled condition of the patient. In one case severe sciatica was complained of for weeks after an injection.

If other measures had failed, and for any reason we were inclined to give this treatment a further trial, we would use neo-salvarsan, because of the greater facility of dealing with it, and its less toxicity. Whether we would give it intravenously or intramuscularly would depend on the circumstances of the case.

Our preference would be for intravenous administration in small doses, and this would generally be our choice in hospital practice.

If the symptoms or circumstances of the case were such that we feared the effects of reaction we would prefer intramuscular administration.

We do not attach much importance to the view that intramuscular injection is to be preferred because the drug may be stored in the muscles, and thus afford the body a continuous supply for some time. From what is known regarding the retention of arsenic in the organs in poisoning cases, we hardly think the method of administration can make much difference in this respect.

Many other remedies have been given, and cases have recovered with their use. In regard to all of them, however, we would again lay stress on what we pointed out before, that in a first attack almost anything may cure, provided the patient be under proper conditions; and, further, that the course of the disease varies so greatly that it is inadmissible to draw conclusions as to the efficacy of any remedy from a small number of cases.

Iron.—Iron has been used alone and in combination with arsenic, and in cases where there is no great amount of gastro-intestinal disturbance it may not do any serious harm, but is not needed, as there is plenty of iron stored in the liver. Where, however, there is sickness and diarrhœa it undoubtedly acts as a poison, and should be avoided. There is one period in the course of pernicious anæmia where iron is, however, very useful, and that is when a patient in the course of recovery has attained a low colour index. This apparently means that he has used up all the iron available in the liver and elsewhere and requires more. At that time arsenic is of little or no service.

Red Bone-Marrow.—Red bone-marrow has been given raw, cooked,

dried, and in various extracts, on the assumption that it contains a substance which stimulates normoblastic function. In most of the published cases in which it is said to have been successful it has been given along with arsenic. When we have given it alone, as we frequently have, we have never been able to satisfy ourselves that it had any appreciable effect, although others appear to have been more fortunate. Some years ago a friend reported a case to us which had done exceedingly well with bone-marrow. We found on inquiry that the marrow used was the yellow variety ordinarily supplied by the butcher!

Thorium X.—A few cases have been treated with thorium X. It is administered in water by the mouth or by subcutaneous injection. A quantity corresponding to 20,000 milligram emanations may be given three times daily. A few recoveries have been recorded, but the published results generally are not favourable.

Antistreptococcus Serum.—A great deal has been written from time to time about the value of antistreptococcus serum. Its use was based on the mistaken notion that the disease is due to a streptococcus infection, and in most of the cases of cure by it that have been published, other remedies, such as arsenic, have been used in addition. We have seen one or two cases which recovered under its use alone, but these are mostly open to the objection that we have already stated, that first attacks may recover with almost any measure.

Normal Horse Serum.—We have largely used normal horse serum in cases which did not respond to arsenic, and have given it both hypodermically and by the mouth, and sometimes with very good results. It may be given every day in doses of 10 c.c., apparently with impunity, as we have never seen any symptoms of anaphylaxis, and it should always be tried when arsenic fails. If it be given by the mouth it is well to administer it at a time when the stomach is empty; it may be diluted at the time with normal saline.

Transfusion of Blood.—Transfusion of blood is another time-honoured measure, and has much theoretically to recommend it. It is improbable that the corpuscles themselves are of use in respiratory interchange; they are almost certainly broken down, although we have never seen the hæmoglobinuria which authors have described as a result of the measure. The blood, which should be obtained from a young healthy adult if possible, acts apparently by neutralising the circulating toxin in some way, and it has been found that the actual quantity injected does not greatly influence the result. It is probable that normal horse

serum acts in somewhat the same fashion. We have generally employed the indirect method, in which the blood is received into a solution of sodium phosphate and then injected into the vein of the patient. In a very few cases the result has been brilliant and recovery has followed; in a larger number there has been temporory improvement with subsequent declension, and repeated transfusion has not been successful; while in perhaps the largest number of cases there has been no good result. It is always worth trying, however, as a last resort, if for business or family reasons it is important that the patient's life should be prolonged as much as possible.

Direct arm-to-arm transfusion through a short paraffined glass-tube has also been carried out, but the results seem to be no better than by the indirect method, and it is much more difficult, and, except in skilled hands, more dangerous.

We tried the method of injecting blood intramuscularly in three cases, but as no good result was obtained we have not proceeded further with the measure.

Feasibility of Operations.—The question of the feasibility of surgical operation sometimes crops up in connection with pernicious anæmia.

We recently saw a case where it was complicated by bleeding fibroid tumours. Each hæmorrhage was definitely lowering the blood count. There were megaloblasts and polychromasia, and the red corpuscles numbered 1,370,000; leucocytes, 4400 per c.mm. The hæmoglobin percentage was 36, giving a colour index of 1·3.

We advocated operation, and hysterectomy was successfully performed. A week after operation the red corpuscles numbered 1,600,000, and the hæmoglobin amounted to 43 per cent.

In another case, a lady, the subject of pernicious anæmia, underwent an operation for gall-stones, when her red corpuscles numbered 3,500,000 and her hæmoglobin percentage was 72. She made a good recovery from the operation, and the course of the anæmia was not prejudiced.

Such cases seem to show that the subjects of pernicious anæmia stand operation surprisingly well, but it is certain that operations may only be performed when the reasons for them are very urgent.

Splenectomy.—Some recent cases have been treated by splenectomy. The subject is treated in an appendix.

CHAPTER XV

CHLOROSIS

Definition.—Chlorosis or green-sickness is a disease affecting young women, most commonly between the ages of fifteen and twenty-five, associated with breathlessness, lassitude, pallor of a peculiar type, and certain changes in the blood.

Etiology.—Chlorosis is a disease of the female sex. Cases of anæmia in males have on several occasions been recorded as instances of chlorosis. While the symptoms and blood changes may show a close resemblance, we agree with von Noorden that the sex gives the disease its distinctive characteristics. Age is an important factor. The disease usually begins between fourteen and twenty, very rarely earlier and sometimes later. Anæmia developing after twenty-five for the *first* time must not be diagnosed as chlorosis without very substantial reasons. On the other hand, *recurrences* of chlorotic attacks may be met with comparatively late in life. The disease often attacks several members of the same family, and girls in large families seem specially liable. A history of chlorosis in the mother is often obtained.

Exciting Causes.—In a small proportion of cases anything in the nature of an exciting cause is sought for in vain, and the predisposing factors and heredity seem to offer the only explanation of the illness. It is, however, more common to find a history of bad hygienic conditions. Want of light and fresh air, and overwork are frequent antecedents. In a few cases want of exercise is the outstanding factor, but the disease is more often due to excessive fatigue than to too little.

Want of proper food is an important cause of chlorosis. Actual privation may be found, but more frequently the condition is due to an indiscreet dietary. Girls of the chlorotic age often show a distaste for flesh food, and prefer articles of diet of a less nutritious character. Capriciousness and irritability of appetite often lead to a large consumption of sweetmeats, milk, buns, and biscuits at odd times, with the

result that meals are toyed with and the total intake of nourishment is insufficient in quantity and unsuitable in quality. Dyspepsia and constipation may add to the effect. Menorrhagia appears to be an exciting cause in a few cases. Mental worry and home-sickness have been thought to give rise to the disease.

The condition is extremely common in domestic servants and in factory workers, especially if they have recently come from the country to live in towns, but it is by no means confined to the poorer classes. It is common enough in wealthier families, though one seldom sees in them the severer cases met with among the poor.

There seems to be little doubt that chlorosis is becoming a less frequent condition than formerly. This may be ascribed to improved hygienic conditions in the kitchen and in the factory and to the passing of the sampler and the "accomplishments" in favour of outdoor sports among girls higher in the social scale.

Pathology.—Chlorosis is not a fatal disease, hence little is known of its morbid anatomy. Dilatation and fatty degeneration of the heart and dilatation of the stomach have been found, but there are no data regarding the condition of the very organs that it is most desirable to know about.

The outstanding facts concerning the blood (which will be discussed later) are the comparatively slight diminution of red corpuscles per cubic millimetre, the low percentage of hæmoglobin, and, according to Lorrain Smith, a very large increase of the total amount of plasma in the body.

A very large number of theories have been advanced in order to explain the nature of the disease. Among these may be mentioned the following:—

1. That the condition is due to a congenital hypoplasia of the heart and vessels.

2. That it is associated with a congenital hypoplasia of the genital organs.

3. That it is due to indigestion, intestinal putrefaction, gastroptosis caused by corsets, or to constipation.

While any or all of these may be of some importance in determining the onset of an attack of chlorosis, they do not explain the condition. The evidences of increased intestinal decomposition are wanting. Constipation is not specially common among chlorotics, and the disease is

not cured by purgatives. There is no evidence of increased blood destruction.

4. That it is due to loss of blood in the form of multiple minute hæmorrhages, especially in the intestinal mucous membrane, and loss of blood by menstruation.

Such a view is difficult to disprove, but there seems just as little in its favour as against it.

5. That the symptoms are an expression of neurosis.

6. That the disease is due to an infection. The slight increase of splenic dulness appears to be the only reason for this suggestion, but it would be suprising indeed in these days if it had not been put forward.

7. That it is due to a functional weakness or deficiency of the bone-marrow. In connection with this view it has been suggested that the marrow may prove unequal to supplying the loss of blood which takes place when menstruation is established. Along with this loss there is often an insufficient intake of iron in the food. It has further been suggested that there may be a loss or disturbance of an internal secretion (probably derived from the ovaries) which is supposed to stimulate the bone-marrow in ordinary circumstances. Polzl[1] has recently shown that there is an increase of red corpuscles before each menstrual period.

8. Lorrain Smith has found, as the result of observations with the carbon monoxide method, that the total amount of blood plasma is greatly increased, and there may actually be an excess of red corpuscles and hæmoglobin in the body although the amount per unit of plasma is deficient.

The last two views require further consideration.

Bone-Marrow Deficiency.—This may be regarded as the classical view of the nature of the disease, and it certainly accords well with the known facts. In its favour is the fact that the disease begins at an age when a special strain is being put upon hæmatogenesis, and an attack often follows unhygienic conditions. The symptoms and course accord closely with the deficiency of corpuscles and hæmoglobin in a unit of plasma.

The small size of the red cells, their poverty in hæmoglobin, the absence of polychromasia, and the rarity of nucleated red cells, as well as the reduced percentage of polymorphonuclear cells, all point in the direction of insufficient activity on the part of the bone-marrow.

[1] *Münch. med. Wochenschr.*, 1910, 333.

The ready curability of the disease with iron is more easily explained on this hypothesis than on any other.

Excess of Plasma.—Lorrain Smith[1] regards an increase of the plasma as the essential cause of the blood condition and the symptoms. At the same time the total oxygen capacity or total amount of hæmoglobin is approximately normal. Taking into account the increase in the amount of plasma and the number of corpuscles per cubic millimetre, there must be a large increase in the total number of red and white cells in the body. It is regarded as probable that in the earlier stages signs of the increase of plasma are hidden as far as the corpuscles are concerned by an increase in their number. Each one, however, contains less than its full complement of hæmoglobin, consequently the indication of the disease is the diminution in the percentage of hæmoglobin in the blood-unit—the cubic millimetre. It is suggested that the increase of corpuscles is an attempt at compensation in the presence of excessive plasma. There is no such compensation in regard to the hæmoglobin per cubic millimetre. Later the compensation in corpuscles also fails.

The relation of the leucocytes to the increase in volume differs from that of the red corpuscles. They maintain approximately normal numbers because they increase in direct proportion to the increase in plasma. In favour of this view it is pointed out that as a large volume of blood has to be sent round the circulation, greatly increased work is thrown on the heart, and the value of a unit of blood for respiratory exchange is diminished. This would account for the cardiac symptoms which occur in many cases of chlorosis. The increased amount of fluid affords an explanation of the functional cardiac murmurs, which on this hypothesis are caused by overfilling of the chambers of the heart, and a consequent relative insufficiency of the valvular orifices. The tendency to dilatation is of course helped by the anæmia and the consequent malnutrition of the cardiac muscle. While the blood as a whole has a normal capacity for oxygen, the increase in quantity renders it unwieldy as a oxygen carrier, and hence dyspnœa is a prominent symptom.

Among the difficulties which suggest themselves in the way of accepting the view of Lorrain Smith is the incidence of a condition involving an increase of all the constituents of the blood as a sequel of bad feeding or hygiene. The elimination of body fluids is so rapid that it is difficult to understand why such a condition should persist. The great increase of plasma in the vessels (sometimes nearly double

[1] *Trans. Path. Soc. London*, li. 1900, 311.

the normal) might be expected to throw an increase of work on the heart, which should give rise to much more urgent cardiac symptoms than ever occur and a higher blood-pressure than has ever been recorded. The blood-pressure is practically never above normal. It is further difficult to understand, on Smith's hypothesis, why the disease is so amenable to treatment with iron and is not cured by the use of purgatives, and why the body weight tends to increase rather than diminish during treatment.

Apart from any criticism of the method, an important factor in influencing the result appears to us to have been overlooked. That factor is the relationship between the hæmoglobin in the marrow and the hæmoglobin in the circulating blood.

Haldane and Lorrain Smith admit that some of the CO inhaled may be taken up by hæmoglobin in muscle, and that if so the estimated total amount of blood will be excessive. The amount in muscle is, however, negligible. It is surely otherwise with the marrow. In the marrow the proportion of hæmoglobin to plasma is very much higher than in the circulating blood. Error from this source is probably nearly a constant one in health, but in disease the normal relationship between blood and marrow is disturbed. In chlorosis the corpuscles are poor in hæmoglobin. There is no likelihood that the amount of red marrow is diminished, and it is possible that along with a qualitative deficiency there is a compensatory quantitative increase. (Lorrain Smith's view practically postulates this.)

In any case the histology of the blood suggests that the proportion of marrow to circulating corpuscles is increased, and this state of affairs would cause the estimate of total volume of blood by the CO method to be unduly high.

This criticism has recently been confirmed by Dreyer, Ray, and Ainley Walker.[1] They conclude that the CO method as hitherto employed for determining the normal blood volume cannot be relied upon, since the results which it yields are not only out of accord with those obtained by direct methods of estimating the blood, but also exhibit marked disagreements among themselves.

They say that "where the normal ratio between circulating intravascular hæmoglobin and extravascular hæmoglobin is disturbed either by the diminution of the intravascular hæmoglobin or by the increase of extravascular hæmoglobin caused by increased activity of the blood-forming organs, or by the deposit of unusual quantities of hæmoglobin or other CO-combining substances in various organs, the partition co-efficient of CO

[1] *Skandinav. Archiv. f. Physiologie*, 1913, 299.

will inevitably be altered. Accordingly the results obtained can never yield accurate information regarding the actual volume of the blood in conditions of disease affecting the blood. At best it can only give a measure of the total quantity of CO-combining substances in the body."

This is in essence just what we have written above.

These authors also state that it is difficult to escape the conclusion that, owing to the use of the CO method, Lorrain Smith's careful and laborious investigation of chlorosis yielded results which cannot be accepted till new experimental evidence is brought forward to support them.

Symptoms. — Chlorosis may develop very rapidly, even in the course of a few days. More frequently, however, the incipient stage extends over two or three weeks. The first symptom complained of is usually breathlessness on exertion. Fatigue, drowsiness, and palpitation soon develop. Pallor, associated with a peculiar greenish tint, does not usually appear till the blood changes are well marked. It shows first in the lips and conjunctivæ, later in the skin. When the condition has become established a great variety of symptoms may be noted. The temperature seldom rises unless some complication occurs.

Alimentary System. — The amount of disturbance varies greatly. Some patients retain a normal appetite, and these tend to become fat; others lose their appetite and become thin. In either case great caprice is often exhibited in the choice of food. Meat is generally disliked. Sour or acid substances, such as lemons and vinegar, may be taken in large quantities. Starch, dry oatmeal, or sago may be taken, and in some cases tea leaves, chalk, or even earth may be eaten.

The tongue is usually pale and clean, but may be furred and flabby. The stomach is sometimes dilated, and gastric ulcer is a common complication. The total acidity and proportion of free hydrochloric acid in the stomach contents after a test breakfast are practically never below high normal values, and may be considerably above these. Constipation is common.

Hæmopoietic System.—The splenic dulness is often enlarged, but the organ is rarely palpable. Lymphatic glands are not enlarged.

Circulatory System.—The patient complains of breathlessness on exertion. In some cases fainting occurs on slight provocation, and is common after prolonged standing. The pulse is generally rapid. Cold feet and numbness of the fingers from weakness of the peripheral circulation are often complained of. At the same time the vessels are excitable, and patients readily flush. In severe cases there may be

some œdema of the ankles. The area of cardiac dulness is increased, particularly towards the right side. This is due in some cases to dilatation of the heart, but in others it is to be accounted for by retraction of the lungs due to superficial breathing. This pulmonary retraction accounts for the unduly loud pulmonary sounds which are sometimes heard. Examination of the heart by X-rays indicates that it is more frequently displaced by shrinkage of the lung and a high diaphragm than actually dilated. Pulsation is often to be seen and felt in the episternal notch, in the pulmonary area, over the right ventricle, and in the epigastrium.

Cardiac and Vascular Murmurs.—The cardiac murmurs of chlorosis are practically always systolic in time. They are heard most frequently over the pulmonary area, with the point of maximum intensity in the second or third left interspace close to the sternum. Less commonly a systolic murmur is best heard in the aortic area, and systolic murmurs are sometimes heard in the tricuspid area or in the mitral area, usually along with the basal murmur, but sometimes alone. The cause of these murmurs has been much debated.

The most commonly accepted view regarding the basal murmur is that it is due to a want of tone in the arterial wall caused by malnutrition, and is produced by the sudden propulsion of blood into a vessel which is relatively dilated in comparison to its orifice. The tricuspid and mitral murmurs, when associated with basal murmurs, are probably due to conduction, but when alone the possibility of dilatation of the heart to such an extent as to bring about such a relative insufficiency of the valvular orifice as to cause tricuspid or mitral regurgitation must be considered.

The question of pre-existing valvular disease may be a very difficult one, but is eventually cleared up by the result of treatment. Chlorotic dilatation is readily curable.

Arterial murmurs are sometimes heard at a distance from the heart. Venous murmurs are common, and are most easily heard in the jugular veins at the root of the neck, especially on the right side. The murmur takes the form of an almost continuous hum—*bruit de diable.* It is best heard when the patient is in the erect posture.

A similar venous hum may sometimes be heard over the eyeball, over the occipital protuberance, and elsewhere. It is very characteristic of chlorosis, although not strictly confined to it.

Diastolic cardiac murmurs in chlorosis have been described, but occur with great rarity. They are heard in the aortic area, and

are to be accounted for by transmission from the great veins of the neck.

Venous Thrombosis.—This contingency is rare enough to be regarded as a complication rather than a symptom of chlorosis. It occurred in 6 out of 431 of von Erben's cases, and in 5 out of 230 cases recorded by von Noorden. It usually affects the veins of the leg or the brain sinuses. The latter contingency accounts for practically all the fatal cases of chlorosis. Its early manifestations are unfortunately very likely to be mistaken for hysteria.

Some authors have regarded the optic neuritis which occasionally occurs in chlorosis as being caused by thrombosis of the cavernous sinus.

It has been suggested that venous thrombosis is more common in those cases of chlorosis, which are fairly numerous, in which the blood-plates are increased in number, and that they become agglutinated in the capillaries so as to form capillary thrombi, which act as the starting-point of the change in the veins. It is certainly possible in some of the cases with an increased number of blood-plates to find in films long, straight, or curved cylindrical masses of blood-plates which might well have been washed out of capillary vessels. In looking for them special care must be taken not to squeeze the cover-glasses together in making the films.

Respiratory System.—Breathing is hurried, and in a few cases there have been attacks of special rapidity of respiration, but without the accompanying sensations of dyspnœa. The respirations are shallow, and as a result there may be some degree of retraction of the lungs, and the diaphragm is at a slightly higher level than normal.

Integumentary System.—The pallor and the tendency to flushing of the skin have already been referred to. Seborrhœa and acne are commonly found. Urticaria and chilblains are very frequent in chlorotics.

Genito-Urinary System.—The urine is abundant, pale, and has a low specific gravity. Menstrual disturbances are very frequent. Menstruation is usually scanty or in abeyance. Rarely it is increased. Leucorrhœa is fairly common. It is not unusual to get a history of menorrhagia preceding the onset of the disease, followed by amenorrhœa when it is established.

Nervous System.—Muscular power is diminished. Some patients are morose and apathetic, and many such cases may receive but scant

sympathy from their relatives before the fact is realised that the girl is ill. Irritability and hysterical attacks are not uncommon. In severe cases the patient is constantly tired, and so drowsy that she may fall asleep whenever she sits down in a chair. Headache is frequent, and in severe cases, tinnitus, temporary deafness, or blindness is met with. The headache may be constant, or may occur in paroxysms. Optic neuritis sometimes occurs, often without any disturbance of vision. Neuralgias are common. Inframammary neuralgia is perhaps most frequent.

The Blood Changes.—The blood when drawn is pale and watery. The specific gravity varies with the amount of hæmoglobin. No special change has been found in connection with the specific gravity of the plasma or serum. The blood coagulates rapidly although fibrin is not increased.

The number of red corpuscles per cubic millimetre varies considerably. As a rule the number when patients first come under observation is about three and a half millions in severe cases. Not infrequently the number is normal—four and a half millions, or increased up to five and a half or even six millions. On the other hand, low counts are sometimes met with, but numbers below two millions are very rare, and are usually to be explained by the co-existence of some hæmorrhagic condition, such as bleeding piles, gastric ulcer, or menorrhagia.

In cases with high counts it will generally be found that some condition of cardiac debility is present—either an organic lesion, usually mitral, or more commonly chronic cardiac strain or dilatation.

The amount of hæmoglobin is always diminished. The diminution is not only absolute, but there is a great diminution relatively to the red corpuscles—in other words, the colour index is always low. A fairly common relationship is a red count of 4,000,000, with 35 per cent. of hæmoglobin, giving a colour index of 0·43. In untreated severe cases the colour index is very rarely above 0·5, but in slight cases may rise to 0·6.

The following table gives the figures in twelve successive cases seen in an outpatient department:—

Age.	Red Cells per c.mm.	White Cells per c.mm.	Hb. per cent.	Colour Index.
21	3,000,000	4062	15	0·25
21	3,582,400	3125	30	0·42
17	4,270,000	4687	45	0·54
23	4,150,000	3516	25	0·3
15	3,800,000	3125	35	0·46
17	4,500,000	3515	35	0·38
14	3,880,000	2148	35	0·45
16	3,080,000	6586	35	0·57
15	2,938,000	5312	30	0·51
16	3,589,600	6250	35	0·49
23	2,320,000	1870	25	0·54
20	3,200,000	3750	30	0·46

Leucocytes are always decreased in number. The diminution seems to be more marked in the more severe cases. The reduction chiefly affects the polymorphs, so that there is a high percentage of lymphocytes, and the percentage of large lymphocytes is often specially increased. Leucocytosis always indicates some complication.

Blood-plates are always increased in number, and sometimes appear almost as numerous as the red corpuscles. Capillary thrombi composed of blood-plates are sometimes seen in stained films.

The red corpuscles show a distinct diminution in their average size. Their centres are much paler than usual, an appearance which corresponds to their poverty in hæmoglobin. In mild cases there is not much change in the shape of the red cells, but in severe cases they may show great deformity. The poikilocytosis may exceed that usually seen in pernicious anæmia, but the corpuscles are all small and show the central pallor. Nucleated red cells are extremely rare, and only occur in very severe cases. Both megaloblasts and normoblasts have been noticed, but megaloblasts occur so rarely that their presence in chlorosis may be regarded as a curiosity.

If a case be watched throughout its course of development and recovery it will be found that at first the red corpuscles are normal in number, but their complement of hæmoglobin is deficient and they are small in size. At a later stage their numbers diminish and poikilocytosis appears. As the case improves there is a rapid increase in the number of corpuscles, but they remain small and pale, and their normal numbers have been regained long before they become of normal size or contain the proper amount of hæmoglobin.

Course, Prognosis, Complications.—As a rule, those cases which

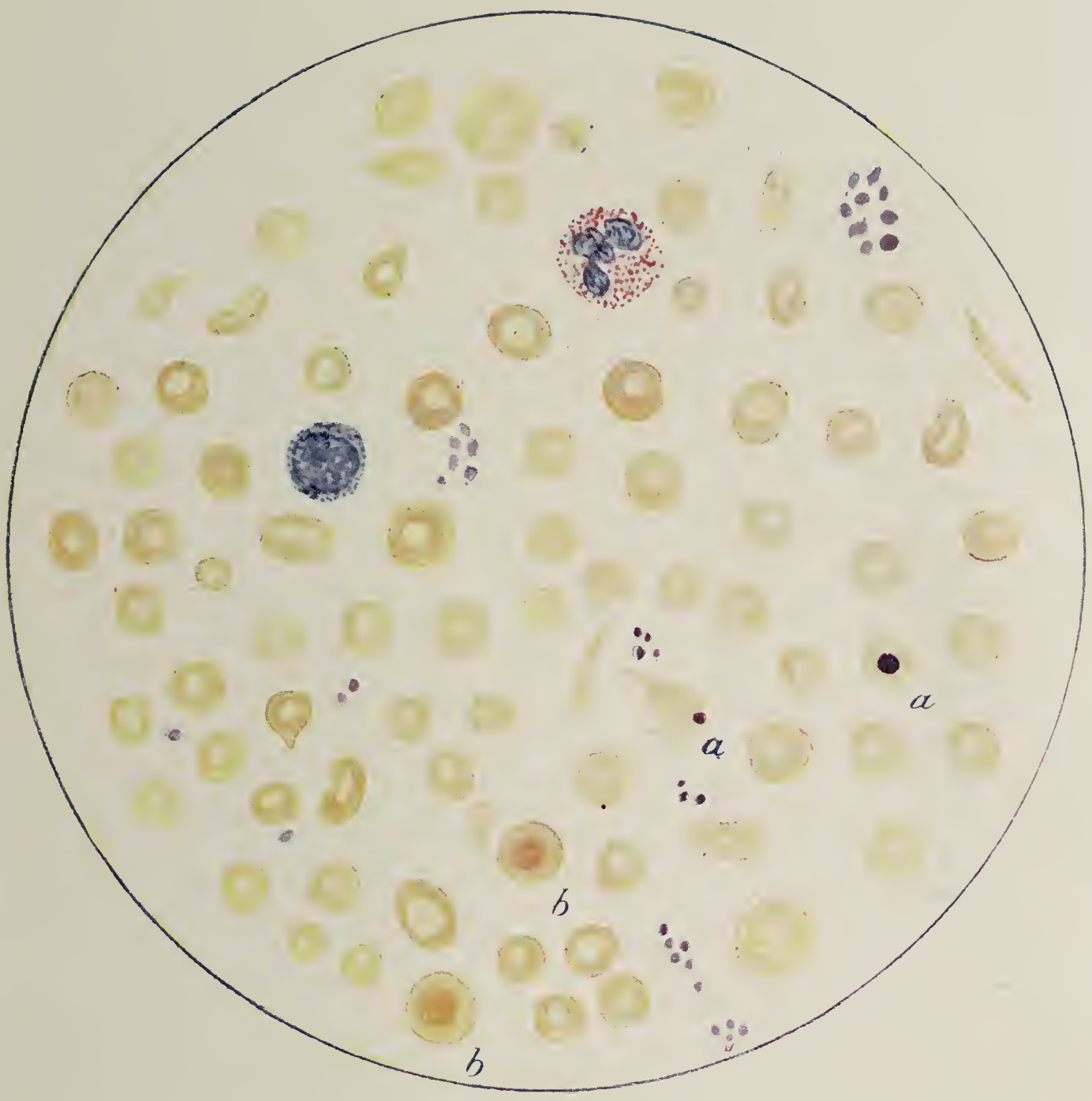


PLATE VIII.—BLOOD FILM FROM CASE OF CHLOROSIS (Jenner's Stain).

The average size of the red corpuscles is diminished.
There is marked poikilocytosis.
Blood-plates are increased. At (*a*) plates are seen superimposed on red cells, an appearance often mistaken for normoblasts.
(*b*) The central condensation of haemoglobin seen in a few erythrocytes.

A. G., *fecit.*

have a rapid onset recover most quickly, but all cases, whether acute or chronic, show a marked tendency to recurrence. In an ordinary case the attack lasts from six weeks to four months, but in a great many cases, although distressing symptoms have disappeared in this time, complete restoration to health has not occurred. An important point in regard to the course of the disease is that patients seldom persist long enough in a course of treatment. They become accustomed to a condition of health which is short of robustness, and hence do not realise the necessity for taking drugs after the more acute symptoms have disappeared. A common result is that a relapse speedily occurs, and it is then found that the relapse does not yield to treatment so readily or completely as a first attack; thus a certain number of these cases fall into a condition of semi-invalidism.

Cases thoroughly treated recover completely, and have not the same liability to relapse that is the fate of those only partially recovered.

The most serious aspect of chlorosis is that if it persists for any time it renders the nutrition of the body imperfect just when development of body and mind should be most active, with the result that both may suffer. Moreover, chlorosis is apt to be attended by complications such as gastric ulcer and thromboses. The occurrence of exophthalmic goitre in cases of chlorosis is probably more frequent than could be accounted for by mere coincidence. There is a greater liability to the infectious diseases, and convalescence from intercurrent disease is prolonged.

Diagnosis.—The clinical picture is usually pretty definite. The outstanding features are the sex, age, the history and general appearance of the patient, the blood changes, particularly the low colour index, and the ready response to treatment with iron. Occasional difficulty arises from an unusual prominence of one or more groups of symptoms. The gastric and cardiac symptoms and those associated with the reproductive system are most likely to lead to error. A very real difficulty sometimes arises in cases where other disease co-exists. Chlorosis has to be distinguished from other conditions causing anæmia. The chief of these are the following:—

1. *Pernicious anæmia* and *leucocythæmia* are readily distinguished by the blood-picture.

2. *Anæmia from Intestinal Parasites.*—The colour index is not likely to be so low as in chlorosis, and in many of the worm infections there is eosinophilia. The fæces should be examined for the eggs of the parasites.

3. *Anæmia from Malignant Disease.*—The type of anæmia is often chlorotic. Malignant disease is not very common in young girls without causing symptoms or physical signs, but may occur. Nucleated red cells are more common and more numerous in malignant disease than in chlorosis, and in the former there is likely to be some degree of leucocytosis, while in the latter the leucopenia and high lymphocyte percentage will be distinguishing features. The colour index is rarely so low in malignant disease as in chlorosis. The difficulty may only be cleared up by the result of treatment.

4. *Anæmia from Chronic Concealed Hæmorrhage.*—The bleeding may be from piles, and patients may not know of these or may not mention their existence without a direct question. More commonly the bleeding is from a gastric or duodenal ulcer, and the blood is so altered that the patient does not recognise it. The diagnosis here may be difficult. The red cell count is likely to be lower in the case of ulcer, the colour index higher, and from time to time a post-hæmorrhagic leucocytosis may be present. The stools should be subjected to the benzidine test for blood.

5. *Tuberculosis.*—Cases of early phthisis and other forms of tuberculosis not infrequently present symptoms and a general appearance which can very readily be mistaken for chlorosis. Error frequently does arise simply because chlorosis is taken for granted and the lungs and other organs are not examined with sufficient care. In difficult cases the examination of the blood may help, but the character of the anæmia tends to be pretty much the same, and the leucocytes undergo the same change in the two conditions. The low colour index of chlorosis is the chief distinguishing point. It is, of course, to be borne in mind that chlorotic girls may become infected with tuberculosis.

The temperature does not give much help, since it is not always raised in early tuberculosis, and it is sometimes (if rarely) raised in cases of chlorosis. One or other of the tuberculin tests may have to be employed in order to clear up the diagnosis.

6. *Kidney Disease.*—Chronic nephritis always causes anæmia in young subjects. The history and a careful examination of the urine distinguish the two conditions.

7. *Pregnancy.*—Early pregnancy should be borne in mind as a cause of anæmia and amenorrhœa.

Treatment.—1. *Prophylactic.*—The prophylaxis of chlorosis largely resolves itself into the application of hygienic principles to girls of the chlorotic age. In families where the mother or elder sisters have

suffered from chlorosis, special care should be exercised in the case of the younger sisters. Sufficient and not excessive exercise, plenty of fresh air and good food, are the important considerations. A timeous holiday and change of air may forestall several weeks of indifferent health. The administration of iron as a prophylactic measure is probably worse than useless. It is of no advantage to a healthy girl to take iron, and if her tissues are habituated to it, it may fail to do good when it is required.

2. *General.*—Sunlight and fresh air are essential. Rest is also a factor of the greatest importance, even in the comparatively rare cases where deficient exercise may have had a causal effect. All severe cases should be kept in bed, and where circumstances permit, even cases of moderate severity are better treated in bed than out of it. To be more explicit, it may be stated that all cases with a percentage of hæmoglobin less than 60 should be kept in bed. The strain on the heart is at once relieved, and the symptoms of dyspnœa, faintness, headache and neuralgia very speedily disappear. They just as readily return, however, so that it may be well to inform patients at once that they are to be kept in bed for three weeks. This period may be curtailed or extended as the blood examination indicates, but will be found a fairly satisfactory average. In most cases it will be some weeks longer before the girl is thoroughly fit to return to work, but unfortunately advice to this effect is too often disregarded. In the less severe cases, and in the convalescent stage in the more severe cases, patients should avoid fatigue and excitement and keep early hours. When the patient has no work to do, a walk in the open air, short of fatigue, should be insisted upon. The more active forms of exercise and games should be interdicted. Cold bathing should be avoided.

Regularity of meal times must be insisted upon, and a special diet may have to be arranged. Sometimes the craving for special and often unsuitable articles of diet and the habit of eating between meals may be best overcome by ordering relatively small meals at a shorter interval than usual, say, every three hours. The chief consideration is to get the patient to ingest a sufficient quantity of protein, and some firmness may be required in order to overcome the almost invariable dislike for meat which chlorotics evince. A small but increasing quantity may have to be definitely ordered at first. When gastric disturbance prevents the taking of solid food, milk, with the addition of an equal quantity of cream, may be advised. This prescription, however, requires supervision, as the milk diminishes the appetite for other kinds of food and

the total amount of food taken may be insufficient. In the case of fat patients and those with a good appetite for solid food, a large amount of milk should not be given. A little alcohol, which stimulates the appetite and favours fat formation, may be given to thin patients. The bowels must be carefully regulated. Iron has a slight tendency to cause constipation, and chronic constipation is very common in girls of chlorotic age. Cascara or aloin are among the most serviceable drugs in this connection. The aloes and iron pill is very useful, given at night in sufficient dose to secure a proper action, while at the same time Blaud is being taken after meals. In some cases a bitter tonic before food, or gastric sedatives such as bismuth or soda, may be required as a preliminary measure, especially if the stomach is sensitive to the administration of iron.

3. *Special.*—Whatever view may be taken of the pathology of the disease, there is no doubt that iron cures chlorosis in the great majority of cases, and that no other drug has even approximately the same beneficial effect.

It is to be noted that iron does not cure chlorosis by replacing iron lost or diminished in the blood. There is an ample supply of iron for this purpose in the protein constituents of the food, but good food and rest alone will not cure chlorosis.

All preparations of iron, whether organic or inorganic, are transformed in the stomach into ferric chloride. There is no doubt, however, that the inorganic salts are much more efficacious than the organic in bringing about a speedy cure.

Owing to a mistaken notion that inorganic iron is not absorbed, numerous preparations of organic iron have been placed upon the market. These, perhaps on account of their similarity to the food-iron, are not nearly so useful as the inorganic salts. Moreover, some of them after all contain so small a proportion of iron that enormous doses would be required to supply the 15 to 20 grains which is the minimum amount of metallic iron which should constitute the daily dosage.

The organic preparations may be divided roughly into two classes —(1) Those which consist mainly or entirely of hæmoglobin, usually derived from ox blood, kept in solution and with preservatives added, or dried. (2) Those which consist of iron in combination with some albuminate, peptonate, or other protein derivative. To some of both of these varieties—it is needless to say that they are all proprietary and often "elegant" preparations—strychnine, arsenic, etc., are added

in small doses. The first class are so disappointing that we have long ceased even to experiment with them. Some of the second class are more useful, as they do contain a fair amount of iron, and are well borne by delicate stomachs and intestines, and in very mild cases of chlorosis they are occasionally useful. Good results have been published with them, but we have never been similarly fortunate. In a recent case of very severe chlorosis (reds, 3,000,000 ; hæmoglobin, 28 per cent.) we gave one of these preparations in full doses for a fortnight. The patient's general condition did not improve, though she was kept in bed all the time, and the count and hæmoglobin at the end of the fortnight were the same. Blaud's pill was then given, and at the end of the next fortnight the reds were 4,200,000, hæmoglobin 63 per cent.

The only condition in which the organic preparations of iron appear to have a special application is in those rare cases in which we fail to find an inorganic salt which the stomach will tolerate. They are useful also in secondary anæmias from chronic intestinal catarrh, and in such conditions as mucous colitis.

Of the inorganic salts of iron the one which is most used and which is probably about the best is the carbonate in the form of Blaud's pill or the saccharated carbonate. A common and good plan is to give Blaud's pill as a capsule, of two or three pills strength. It is not astringent, and is generally well borne. Reduced iron is very useful, and its small dose is an advantage. It should be obtained free from sulphur as an impurity, otherwise unpleasant eructations of sulphuretted hydrogen may result.

The sulphate and perchloride of iron are astringent, and are not well tolerated by patients with irritable stomachs, but when they can be taken very satisfactory results may be obtained. The scale preparations are usually easily taken. Their disadvantage is the small proportion of iron they contain. The dosage is important, and should be carefully regulated. The common error is that too little iron is taken. The equivalent of two Blaud's pills three times a day after food should be prescribed to begin with. As long as there is no gastric disturbance one pill may be added every second day till from twenty to twenty-four per day are being taken. The maximum should then be persevered with for some weeks, and then gradually diminished before being left off. The effect of the iron should be noted by repeated examination of the blood. As long as the percentage of hæmoglobin continues to rise the iron may be continued. If it becomes

stationary before the normal 90 per cent. is reached it is better to leave off iron for a few weeks and then begin again with the smaller doses. Generally speaking, we find it well to give iron for two months at first, then stop for three weeks, then give it for six weeks, and so on. If it is given uninterruptedly for long periods the system seems to get used to it and it ceases to do good. The iron should always be taken regularly and without interruption. Even when dyspeptic symptoms are complained of the iron should not be too readily withdrawn or diminished. The dyspepsia is more likely to be due to the chlorosis than to the iron. It is often found that patients who believe they cannot take iron can do so without difficulty if they are confined to bed.

In cases where iron disagrees in spite of changes and mild gastric sedatives, chalybeate waters may be tried. When iron is well borne but fails to do good it may be combined with or replaced by arsenic. The latter is likely to succeed best in cases where the red corpuscles are considerably diminished. It should be given in initial small doses and gradually increased. Occasionally a few doses of digitalis seem to initiate improvement after iron alone has falied.

It may be well to point out that many preparations of iron particularly in the form of pills, are quite useless.

Some cases have been recorded in which bleeding has been resorted to with a view of stimulating the bone-marrow, and a certain measure of success seems to have followed this procedure. The amount withdrawn is about 4 ozs. Measures directed towards the withdrawal of fluid from the body by dry diet, sweating, and free purgation do not cure the disease, and do not appear to shorten the period of cure by means of iron.

The standard by which a cure is to be determined is the condition of the blood and not merely the appearance of the patient.

CHAPTER XVI

SECONDARY ANÆMIA—SYMPTOMATIC ANÆMIA

Anæmia may arise from a very large number of causes. Symptomatic anæmia may be divided into—1. Acute post-hæmorrhagic anæmia, and 2. Simple secondary anæmia.

1. Acute Post-Hæmorrhagic Anæmia

Causes.—Hæmorrhage may take place—

(*a*) From wounds in any part of the body;

(*b*) From rupture of vessels, aneurysm, or varicose veins;

(*c*) From gastric or duodenal ulcer, œsophageal or gastric veins in cirrhosis of the liver, hæmorrhoids, typhoid ulcers;

(*d*) From various parts of the body in the bleeding diseases, hæmophilia, purpura, scurvy, pernicious and other anæmias and leucocythæmia;

(*e*) From the nose or respiratory tract;

(*f*) From the urinary passages;

(*g*) From tubal abortion, and a variety of uterine conditions.

Symptoms.—An early sign is pallor of the skin, lips, and conjunctivæ. This pallor is seen before the loss of blood is very great, and is accounted for in part by psychical conditions. No other condition occasions so much anxiety, and there may be great weakness, giddiness, and faintness, subjective sensations of smell, sound, or flashes of light, or even blindness. There are cold sweats and an increased secretion of urine. Palpitation is noticed, and is followed by weakness of the heart and feebleness of the sounds.

The pulse changes rapidly in volume and tension and soon becomes somewhat irregular, and the pressure is low and volume small. Fainting is often seen at this stage.

Respirations become superficial, and sighing is frequent. There may be hiccough, nausea, and even vomiting. Symptoms become more severe owing to loss of fluid. Sweating stops, the skin becomes dry,

the eyes dull. Syncope becomes more persistent. In the conscious intervals there may be aphasia or paraphasia; the voice is weak. Fibrillary tremors may be seen, and delirium and convulsions may follow.

If the hæmorrhage is checked before a fatal result takes place the patient is not yet out of danger. The blood is diluted by fluid from the tissues, and it is probable that the hydræmia leads to a destruction of some of the less resistant corpuscles.

The Blood Changes.—As blood is lost coagulability increases, so that at the end of a big hæmorrhage clotting may be almost immediate. Whenever blood is lost to any appreciable extent the body fluids pass into the plasma, so that the blood is diluted. In severe cases the red cell count may fall almost at once to less than one million per c.mm. Hæmoglobin is of course reduced proportionately until regeneration begins. The maximum degree of anæmia is generally not reached till from one to three days, or even longer, after the bleeding. If the hæmorrhage be survived regeneration begins almost at once. Young red cells, poor in hæmoglobin, are passed out from the bone-marrow, so that the colour index falls, it may be as low as 0·5. The red corpuscles are small, and show great inequality in size and a moderate amount of distortion. There is very marked polychromasia, and a small number of the corpuscles may show punctate basophilia. On the second or third day nucleated red cells appear. These are normoblasts exclusively in most cases, but if there has been great marrow disturbance a few megaloblasts may also be found. Occasionally after hæmorrhage sudden accessions of normoblasts to the circulation (blood crises) occur.

White Cells. — Immediately after hæmorrhage an increase of the polymorphs in the circulating blood takes place. The leucocytosis is not very large, and after a single hæmorrhage it is of short duration, often disappearing within eight hours, though it may persist for three or four days. After a large hæmorrhage the blood-plates are always increased. The blood examination may throw light on symptoms otherwise obscure, as in the case of ruptured aneurysm or ruptured ectopic gestation, or internal hæmorrhage after injury.

Course and Prognosis.—As already indicated, the maximum severity of the anæmia is not reached till some days after the actual hæmorrhage. It is quite impossible to say to what extent hæmorrhage may occur

without being fatal. Its suddenness, the age and strength of the patient, are important varying factors. We had one case of hæmatemesis in which the red corpuscles fell to 400,000 per c.mm. in two days, and recovery followed.

The rate of regeneration will depend on the extent of the blood loss and the age and nutrition of the patient. A moderate hæmorrhage in a young healthy adult will be made good in a few days. After most surgical operations in comparatively healthy persons there is no anæmia after ten days.

After very severe or repeated hæmorrhage regeneration will require a month or six weeks, but this would be a modest estimate for weakly or elderly patients or cases in whom some degree of bone-marrow exhaustion had supervened. Infants and young children bear hæmorrhage badly, but in cases which survive, regeneration is particularly rapid after the first few days.

Treatment.—The first indication is, of course, to arrest the hæmorrhage by appropriate measures. The symptoms may then be met by lowering the head, slaking the thirst, and making the patient as comfortable as possible. If the hæmorrhage has been definitely arrested a stimulant will do good, and will be most grateful to the patient. It must be withheld, however, unless death is threatening, in cases where there is risk of a return of the bleeding.

Severe symptoms due to loss of fluid may be met by bandaging the patient's limbs, by transfusion of blood or of physiological saline solution. It is doubtful if transfusion of blood has any advantage over saline transfusion, and the latter, being more simple, is to be preferred.

Injections into the rectum may be retained and absorbed and sometimes suffice, but in more urgent cases the transfusion must be into a vein. Injections are sometimes made into the loose fibrous tissue of the axilla or elsewhere, but are painful and probably not so efficacious as the intravenous method.

The after-treatment consists of confinement to bed, careful dieting, since the stomach is often very irritable for several days or even weeks, such symptomatic measures as may be indicated, and the administration of iron on the lines suggested in the case of chlorosis (Chap. XV.).

2. Simple Secondary Anæmia

Causes.—The causes of secondary anæmia are very numerous, and may be grouped as follows:—

(1) Repeated hæmorrhage.

(2) Active hæmolysis, from such conditions as cholæmia, severe sepsis, and malaria.

(3) Disturbance of the balance between production and elimination of red corpuscles. The lives of the red corpuscles may be shortened by a variety of adverse conditions, and the same conditions affecting the marrow may lead to the output of corpuscles with diminished resistance. Among these conditions are—

(*a*) Toxic conditions, *e.g.* sepsis, fevers, syphilis, malignant disease.

(*b*) Improper nourishment and unfavourable surroundings.

(*c*) Exhausting disease such as Bright's disease, chronic catarrh of the alimentary tract and consequent loss of mucus and epithelium, lactorrhœa, and the various conditions discussed in Part IV.

Symptoms.—The symptoms are often largely masked by those of the causal condition. In an uncomplicated case there is very great pallor. Patients look very white and have none of the greenish colour of chlorosis or the yellowish tinge of pernicious anæmia. A patient suffering from secondary anæmia with two million corpuscles per c.mm. always looks far more anæmic than a patient suffering from pernicious anæmia with one million.

The appetite is greatly impaired and all the digestive functions are at a low level. Owing to deficient oxidation there is fatty degeneration of the organs. The heart acts feebly, its rhythm may be irregular, there are hæmic murmurs. Fainting may occur with sudden changes in posture; there is often palpitation and dyspnœa on slight exertion. The blood-pressure is not diminished, unless there is considerable cardiac weakness.

Œdema about the ankles may occur, probably due to the hydræmia. There is sometimes albuminuria. Spontaneous hæmorrhages, chiefly in the form of petechiæ, sometimes occur, but are not common, and are possibly accounted for by fatty change in the vessels.

Nervous symptoms may develop. Patients are often querulous or irritable. Actual lesions have been found post-mortem. Among these have been atrophy of ganglion cells and deficient staining of Nissl's granules.

Blindness occasionally occurs, due sometimes to no discoverable lesion, sometimes to actual optic neuritis.

The Blood Changes.—The chief blood changes may be very diverse according to the nature of the cause, and a special part of this book is devoted to a description of them from the etiological standpoint. The changes common to all and representing uncomplicated anæmia are similar in the main to those of acute hæmorrhagic anæmia. Poikilocytosis is likely to be more marked. Nucleated red cells are less numerous, unless just after a fresh hæmorrhage in a case of not too long standing. The leucocyte reaction is also less. In chronic hæmorrhagic anæmia there may even be leucopenia. In a long standing case there may be a few myelocytes in the circulating blood.

Significance of the Blood Changes.—The diagnostic value of blood examination may be considerable. Cases of weeping aneurysm, bleeding piles, and gastric or duodenal ulcer may be cited as examples, and treatment might be influenced after traumatic or other hæmorrhage by a knowledge of its extent.

The blood count rather than the symptoms may occasionally give a clue to the diagnosis of many cases of repeated hæmorrhage; and granted that anæmia of a secondary type is found, careful investigation of possible sources of hæmorrhage must be made.

Among causes of anæmia which are specially common and frequently overlooked are bleeding piles, menorrhagia or metrorrhagia, duodenal ulcer, and worm infections.

Treatment.—After repeated hæmorrhages the reaction on the part of both red and white cells is not so brisk as after a single hæmorrhage, and patients who become anæmic from such causes as bleeding piles, fibroids, etc., may require careful and prolonged treatment before the blood returns to its normal condition.

Mikulicz, many years ago, advanced the view that surgical operations should not be undertaken when the hæmoglobin percentage is less than 30. This is probably as reasonable a general law as can be laid down in medicine. We can quote one case where hysterectomy for bleeding fibroids was performed when the hæmoglobin percentage had fallen to 24. The patient did well. In another case of the same nature hysterectomy was performed when the red cell count was 2,000,000, hæmoglobin 30 per cent. In a fortnight after operation the red corpuscles numbered 2,900,000, the hæmoglobin amounted to 50 per cent. It should be remembered that in skilful hands hysterectomy is practically a bloodless operation. In chronic gastric and duodenal ulcers and similar conditions with slowly advancing anæmia,

surgical aid, to be of service, must be invoked before the hæmoglobin percentage has fallen to 30 or even 40.

The treatment of secondary anæmia, apart from the treatment of the cause, is to be carried out on the lines laid down in the treatment of chlorosis (Chap. XV.).

CHAPTER XVII

APLASTIC ANÆMIA

This condition is characterised by a very marked reduction of red corpuscles and an absence of the blood changes associated with regeneration in the bone-marrow.

Etiology.—The majority of the cases have occurred in patients under forty years of age. Under twenty and over forty the condition is much less common. In the majority of cases there is no discoverable cause, but the condition has followed bothriocephalus infection, pernicious anæmia, syphilis, albuminuria, and endometritis. A history of severe or repeated hæmorrhages is common, and it may follow severe septic and toxic conditions.

Pathology.—There is some fatty degeneration and the usual accompaniments of anæmia. The liver and spleen sometimes give a slight iron reaction. The spleen is generally fibrous, the Malpighian corpuscles are small, and cells are scanty in the pulp. The lymphatic glands contain comparatively few free cells. The bone-marrow, even in the flat bones, is pale. The marrow in the shafts of the long bones presents the characters of ordinary yellow marrow, except in some instances for a few small scattered red islands.

On microscopic examination areas of marrow may show gelatinous degeneration. In large areas there may be nothing but fat and fibrous tissue, but in the red islands blood-cells are found; these are for the most part lymphocytes. A few red cells are seen in scattered areas; among them are normoblasts, and, in some cases, a good many megaloblasts. Many of them show karyorrhexis and other indications of degeneration. There is sometimes polychromasia and basophilic stippling.

Granular cells are very scanty in the marrow, but islands of myelocytes may be found. There are also lymphoid cells showing a transition from the myeloblast to the myelocyte. Eosinophils are very rare. Giant cells are scanty or altogether absent in sections. Phagocytes con-

taining red cells and pigment can often be demonstrated. A remarkable increase of basophil leucocytes not only in the marrow but throughout the fibrous tissues has been seen in a few cases.

The condition appears to be due to an exhaustion of the bone-marrow, or an inability to respond to calls upon it. We have seen it in several instances in which death has followed repeated or continued hæmorrhage. It also follows severe septic and toxic conditions. In some cases the aplasia appears to be due to the severity of the toxin, so that regeneration never takes place. In other cases regeneration may first occur and then fail. In the cases in which no causal condition can be discovered there may be an inherent vulnerability or weakness of the marrow which renders it unable to respond to even a slight extra demand upon its functions.

Aplastic anæmia may apparently occur as a last stage in pernicious anæmia.

Symptoms.—The symptoms are those usually found in severe anæmia, and need not be repeated. In many cases there is a tendency to hæmorrhages from the gums and mucous membranes, and purpura is often seen. There is no special tendency for any enlargement of the liver, spleen, or lymphatic glands to take place.

Blood Changes.—The blood looks pale. Rouleaux formation is deficient. The red cells are greatly diminished in number. Counts under one million are fairly frequent, and even lower counts have been noticed. There is generally a diminution in the average size of the red corpuscles. Poikilocytosis may be marked. A fair number of megalocytes are sometimes present. Polychromasia is generally absent, and is never very marked. Normoblasts are sometimes noted in very small numbers. Megaloblasts are even more rare, except in cases occurring in children. Both forms of nucleated red cells, if they have been present, disappear as the case advances.

The colour index is generally rather low, but in a few cases it has been over 1. This is doubtless due to a certain amount of megaloblastic regeneration in parts of the marrow, so that megalocytes are turned out into the circulation. Too much stress, however, must not be laid upon observations on the percentage of hæmoglobin, as it is very difficult indeed to make accurate estimations when anæmia is extreme.

It is extremely difficult to make a certain diagnosis during life

between aplastic anæmia with a high colour index and pernicious anæmia. The absence or disappearance of nucleated reds in the former case, and their tendency to increase in the latter case as the disease progresses, is usually suggestive.

The number of leucocytes is almost always diminished, and certainly always towards the close of the case. The reduction chiefly affects the cells of the granular series, except that basophils may be more numerous than usual. Lymphocytes are always present in high percentages, and are often the most numerous white cell in the blood. Blood-plates are diminished in number.

The following cases[1] may be quoted:—

	Sex.	Age.	Red Corpuscles.	Colour Index.	Leucocytes.	Polymorphs.	Lymphocytes.	Eosinophils.	Basophils.	Myelocytes.	Normoblasts per c.mm.	Megaloblasts.
Steinhaus and Stordeur	F.	43	2,000,000	..	5,000	25	75	0	..	..	..	..
,, ,, ,,	M.	27	1,960,000	0·8	2,700	31	69	0	..	..	0	..
Carslaw and Dunn	M.	24	1,008,000	1·0	4,800	19	77	0	0	4	24	..
	(later)		650,000	1·1	2,000	16	78	0·5	0·75	5	0	..
Barberis	F.	..	2,200,000	0·6	4,600	..	..	0	..	..	..	..
Herz	,,	24	330,000	1·5	1,600	33	67	0	0	0	0	..
,,	,,	32	1,600,000	0·9	5,600	50	49	0	0	0	0	..
	(later)		380,000	1·3	2,600	77	21	1	0	0	0	..
Authors	F.	68	1,200,000	1·25	4,000	48	51	0	1	0	0	Very few.
P.M. *no* increase of red marrow in femora, ribs, or sternum. History of anæmia only three weeks before admission. In hospital ten days.	,,	,,	1,300,000	1·15	3,200	35	62	0	3	0	0	0
	,,	,,	1,700,000	1·1	10,000	83	13	2	0	2	0	0
	,,	,,	800,000	1·25	4,400	49	51	0	0	0	0	0
	,,	,,	900,000	1·0	8,000	64	34	1	1	0	0	0
Authors	F.	32	625,000	1·17	2,200	..	..	..	..	..	0	0
P.M. *no* increase of red marrow.. History of slowly progressive anæmia for two years. In hospital seven weeks.	,,	,,	560,000	1·4	1,200	36	63	1	0	0	0	0
	,,	,,	715,000	1·23	1,500	..	..	..	..	..	0	0
	,,	,,	980,000	1·1	2,600	..	..	..	..	..	0	0
	,,	,,	550,000	1·4	3,700	..	..	..	..	..	0	0
	,,	,,	330,000	1·4	3,500	..	..	..	..	..	0	0
	,,	,,	340,000	1·4	3,600	..	..	..	..	..	0	0
Authors	M.	19	960,000	0·8	16,900	70	30	0	0	0	0	0
P.M. *no* increase of red marrow. Hæmatemesis for fifteen days before death; quite healthy before. Numerous ulcerated areas in stomach.	,,	,,	720,000	0·8	12,000	65	34	1	0	0	0	0
	,,	,,	800,000	0·75	6,000	..	..	..	..	..	0	0

Diagnosis.—The diagnosis depends upon the blood examination, but often cannot be made with certainty during life.

Prognosis.—In many cases aplastic anæmia is simply the terminal phase of a serious disease. In any case the duration of the condition

[1] For cases and references, see Hirschfeld, *Folia Hæmatologica*, xii. 1 Teil, 1911, p. 347.

never exceeds a few months. It may terminate suddenly by hæmorrhage, or be cut short by some intercurrent disease, such as pneumonia.

Treatment.—The only possible chance of doing good would be the discovery of a removable cause, but even then treatment would be late in the day. In all ordinary circumstances we have to deal with an exhausted marrow, and until an elixir of life is discovered curative treatment is out of the question. The drugs mentioned in connection with secondary and pernicious anæmia might be tried.

CHAPTER XVIII

SPLENIC ANÆMIA—PHAGOCYTIC ANÆMIA

Splenic Anæmia or Banti's Disease

This is a disease of unknown causation, characterised by enlargement of the spleen, anæmia with special blood changes, in the later stages by cirrhosis of the liver with jaundice, and by an exceedingly chronic course.

Morbid Anatomy and Pathology.—The naked-eye changes are those associated with cirrhosis of the liver and spleen, and jaundice.

Spleen.—The capsule is enormously thickened. There is a great increase of fibrous tissue throughout the organ. The Malpighian bodies are atrophied. White cells in the pulp are scanty, and lymphocytes predominate. There is often a large quantity of pigment either in large cells or lying free in the pulp, and a large proportion of this gives the free iron reaction. The arteries are sclerosed and the sinuses are dilated and engorged with blood.

Liver.—The portal spaces show a great increase of fibrous tissue. The fibrous tissue may spread into the liver substance so that the lobular arrangement may be destroyed and small groups of cells may be cut off and strangulated. The fibrous tissue strands show considerable infiltration with leucocytes. Pigment may be found in the capillaries and in the endothelial cells. Pigment is scanty or absent in the liver cells. Some of it, when present, gives the free iron reaction.

Bone-Marrow.—There is usually a certain amount of erythroblastic reaction and some extension of red marrow into the shaft of the long bones. Normoblasts are slightly more numerous than usual, and a few megaloblasts may be seen. Unless there has been some complication there is but slight leucocytic activity, and the majority of the white cells are lymphocytes. Giant cells are often scanty, and are always small and degenerated. Some iron pigment is commonly found in the leucocytes and endothelial cells.

Kidneys.—A varying degree of cirrhotic change has been present in all our cases.

The pathology of the disease is not understood. It has been suggested that it is due to some toxin absorbed from the intestine. Mitchell Clarke suggests the view that it is due to a failure of the eliminative function of the spleen, whereby dead blood corpuscles and their products are allowed to pass through the spleen and set up irritation there and later in the liver. These views fail to explain the improvement that occurs in cases in which the spleen has been successfully removed. It is more probable, as Rolleston suggests, that there is a chronic infective or toxic process located in the spleen.

Sutherland and Burghard[1] suggest that it is due to loss of vaso-motor control of the splenic artery, which would account for the splenic hyperplasia and consequent exaggeration of its function of removing effete blood corpuscles. The increased flow of blood through the splenic artery would lead to distension of the arteries of the stomach and occasional rupture of vessels and hæmatemesis.

Symptoms.—The disease affects young adults, and is most common about the age of thirty. The disease has occurred in more than one member of the same family, and a variety of conditions such as malaria have preceded it, but none of these antecedent circumstances are sufficiently constant to suggest a causal relationship.

First Stage.—At the outset there may be no symptom beyond the mere presence of an enlarged spleen. Attention may be drawn to this by pain set up by perisplenitis; more commonly the enlargement is discovered more or less by accident. Occasionally some weakness or dyspepsia may be complained of. In one case in this stage a very remarkable leucopenia was present, although there were no symptoms of anæmia, and the red cells looked healthy.

Second Stage.—It is usually in this stage that the condition is first observed. The splenic enlargement is now considerable, and the spleen may reach below the umbilicus. Anæmia with the usual symptoms may become a marked feature. Gastro-intestinal disturbance, with sickness and diarrhœa, may become prominent. Hæmorrhages occur in a large proportion of the cases. These are most commonly associated with the alimentary canal, but epistaxis and purpura have been noted with some frequency.

[1] *Lancet*, 24th December 1910.

Third Stage.—The symptoms of cirrhosis of the liver now become added to the existing anæmia. The liver, and to a less extent the spleen, tend to diminish in size. Gastro-intestinal symptoms become marked. Vomiting and hæmatemesis are common. Jaundice is present in varying degree. Ascites becomes a prominent symptom. The tendency to hæmorrhages increases, the anæmia advances, the leucocytes diminish, and there is great weakness and prostration. Death is brought about by a large hæmorrhage, or by toxæmia or exhaustion, or some intercurrent complication.

Blood Changes.—In the first stage leucopenia may be the only alteration in the blood. In the second stage the red corpuscles commonly number two and a half or three millions. Hæmoglobin is reduced rather more than proportionately, so that the colour index is low. The index, however, seldom reaches the very low figure sometimes noticed in chlorosis. In a few cases poverty of hæmoglobin has been the only blood change. There may be some deformity and alteration in size of the red cells. Normoblasts have been found in a majority of the cases, and in a few instances megaloblasts appear. Polychromasia and granular degeneration were a marked feature in one of our cases.

The white cells are never increased, and in the great majority of cases are diminished in number. The diminution may be present at an early stage, and becomes more marked as the disease proceeds. The number per cubic millimetre may be 500 or even less. In the second stage all varieties seem to be affected, so that differential counts are not much disturbed. In the late stages lymphocytes are more affected, and still later the eosinophils tend to disappear.

In one case we found—

Date.	Red Cells.	Hb.	White Cells.	Polymorphs.	Lymphocytes.	Eosinophils.	Basophils.	Myelocytes.
17/3/04	3,848,000	74	2600	57	40	1	1	1
11/5/04	1,840,000	40	800	94	6	...	...	...

The glycogen reaction in this case was well marked.

The blood changes often admirably reflect the extremely chronic character of the disease, and cases have been seen and recorded in which the blood-picture remained practically unchanged after an interval of five years.

In those cases in which splenectomy has been successfully performed the blood has shown those changes which have followed splenectomy for such conditions as trauma.

Diagnosis.—In the first stage it may be impossible to make a definite diagnosis. If there be leucopenia along with the splenic enlargement, and if infection by animal parasites can be excluded, splenic anæmia is the most probable diagnosis. Pallor, jaundice and ascites, greater anæmia and more generalised hæmorrhages, a smaller size of liver and spleen, and a relatively more acute course, distinguished Banti's disease from Gaucher's splenomegaly. The disease differs from the splenic anæmia of infants, which is always associated with leucocytosis (see Chap. XXVII.). The splenic enlargement, the blood changes, and the chronic course distinguish the second stage. The third stage can be distinguished from primary hepatic cirrhosis by the blood changes, and by hæmorrhages not specially associated with the portal circulation,

Prognosis.—In a very few cases spontaneous cure seems to have occurred. Much more commonly the disease is gradually progressive, but there may be sudden exacerbations and prolonged remissions. The risk of intercurrent affections is the greatest danger. Sudden hæmorrhages may occur at any time, but are more common in the later stages. At the best the patient cannot look forward to anything better than a life of semi-invalidism unless a successful splenectomy is performed. It has to be remembered that in a few cases symptoms have persisted after the spleen has been removed.

Treatment.—The diet should be bland and unirritating. In large measure the medicinal treatment must be symptomatic. Benefit has been found to follow the use of arsenic and of quinine. Boric acid has been advocated by Bramwell. X-rays applied to the spleen has caused a return to normal in its size and in the blood condition in some cases. In others there is improvement up to a certain point without further benefit. In yet other cases X-rays have done no good at all.

A sufficiently large number of successful cases has been recorded to justify the removal of the spleen in cases which are not improving under medicinal treatment. The operation, however, is not to be lightly recommended. In a few cases it has been immediately fatal from hæmorrhage; in others there has been fatal gastro-intestinal hæmorrhage after a few days. The danger from hæmorrhage increases with increasing anæmia. Death from pneumonia followed operation in one of our cases, and a fatal result has followed vague gastro-intestinal symptoms some months after the operation.

Literature

Paulicek, *Folia Hæmatologica*, ix. 1 Teil, 1910, 475. Banti, *Folia Hæmatologica*, x. 1 Teil, 1910, 1.

Primary Splenomegaly: Gaucher's Disease

This condition closely resembles Banti's disease as regards symptoms and course. It often affects several members of a family. Hereditary influence is not so common, but cases occurring in father and daughter and in mother and daughter have been recorded. The age incidence is earlier than in Banti's disease, and it is more common in females.

Pathology.—The spleen is uniformly enlarged, and sections have a grey appearance with scattered white patches. Malpighian bodies are small. The pulp shows a great infiltration with large hyaline cells measuring 20 to 40 μ in diameter, with small nuclei, apparently endothelial in their nature and probably derived from the reticulum. Some of the infiltrated areas show necrotic changes. Their distribution suggests an alveolar arrangement. The liver is also enlarged, and in its fibrous tissue are groups of cells resembling those found in the spleen. The lymphatic glands in many instances show fibrosis, and may show patches where there is an invasion of the "Gaucher cells." The bone-marrow may show similar cells either in groups or scattered irregularly. These organs contain granules of yellow pigment, some of which may give the iron reaction. An association with tuberculous lesions has been noticed, but this is probably accidental.

Symptoms.—The spleen is greatly enlarged. Later, the liver enlarges and may reach an enormous size. Ascites is very uncommon. The superficial lymph nodes are not enlarged. Jaundice has been noticed, but appears to be exceptional. More usually the skin shows a brown or a peculiar grey discoloration. A brownish-yellow wedge-shaped thickening of the conjunctiva beginning at the nasal side of the cornea is described by Brill and Mandlebaum. The temporal side shows this change at a later stage. Emaciation becomes a marked feature as the disease advances, but the patient retains a remarkable sense of comfort and well-being for a surprisingly long period. There is usually a hæmorrhagic tendency. There may be spontaneous hæmorrhages from such situations as the gums, and bleeding after tooth

extraction or wounds may give rise to trouble. The blood changes are often not characteristic, but some degree of anæmia always develops sooner or later. Red cells may be diminished to three millions, hæmoglobin is more reduced, and normoblasts may be found. The leucocytes are either unaffected or there may be a slight leucopenia.

Diagnosis.—A history of several members of a family being affected, the presence of pigmentary changes other than jaundice, the early development of enormous enlargement of the spleen and liver, the late incidence of anæmia, the existence of leucopenia and a tendency to hæmorrhage, the eye symptoms and absence of ascites and of subjective symptoms, would strongly suggest this condition.

Prognosis.—The course in primary splenomegaly may be very prolonged. In Gaucher's own case the spleen had been enlarged for twenty-five years. The patient may have little discomfort for a very long time.

Treatment.—General treatment may be carried out on the same lines as in Banti's disease. Brill and Mandlebaum quote eight splenectomies in fourteen cases. Three died as the result of operation, and in one case the liver continued to enlarge. They doubt whether the progress of a disease affecting the whole hæmopoietic system can be benefited by the removal of one organ only; but as more benefit has followed from splenectomy than from any other measure it is probably the best treatment at present available.

Literature

Risel, *Ziegler's Beiträge*, xlvi. 2. Brill, Mandlebaum and Libman, *Amer. Journ. of the Med. Sciences*, June 1909. Brill and Mandlebaum, *Amer. Journ. of the Med. Sciences*, December 1913.

Phagocytic Anæmia

Van Nuys and Rowley have described cases in which there was very marked anæmia, apparently due to a very great phagocytosis of red cells in the circulating blood. All the varieties of leucocytes, including myelocytes and what were taken to be plasma cells, took part in the phagocytosis, and leucocytes were ingested as well as red corpuscles.

In Rowley's case the type of anæmia varied curiously from day to day. At one time there were small corpuscles and normoblasts, with

low colour index, at others there were megaloblasts, large red cells, and high colour index. The number of leucocytes was greatly increased; the normal proportions were not much disturbed, but myelocytes and plasma cells were present. Injection of five drops of the patient's blood into a guinea-pig caused in two weeks' time a marked phagocytosis of the red corpuscles. The phenomenon lasted for nearly two months. The condition is ascribed to the presence of auto-opsonins in the blood.

Hopkins has recorded a case in which phagocytosis developed in the blood of a case of pernicious anæmia after transfusion.

Literature

Rowley, *Journ. of Exper. Med.*, x. 1908. Van Nuys, *Boston Med. and Surg. Journ.*, clvi. 1907. Hopkins, *Archiv. of Int. Med.*, vi. 1910.

CHAPTER XIX

HÆMATOGENOUS CYANOSIS—HÆMOCHROMATOSIS—LIPÆMIA

Hæmatogenous Cyanosis

Apart from diseases of the heart and lungs, cyanosis may be due to changes in the blood. There may be an abnormally high blood-count with enlargement of the spleen (splenomegalic polycythæmia). On the other hand the blood-count may be normal, but there is some alteration in the blood-pigment. The most common abnormal pigment is methæmoglobin. Sulphhæmoglobinæmia also occurs.

Splenomegalic Polycythæmia—Erythæmia

This condition, first described by Vaquez in 1892, is characterised by an increase in the number of red blood corpuscles with cyanosis and enlargement of the spleen.

Etiology.—Most of the recorded cases have occurred between the ages of thirty-five and fifty, but the disease may possibly be congenital in some instances. Nothing more convincing than mental worry has been suggested as an exciting cause.

Morbid Anatomy and Pathology.—Examination of the shafts of the long bones shows that there is an increased activity of red blood corpuscle formation. The yellow marrow is completely, or in large part, converted into red marrow. In some cases the erythroblastic function does not appear very active, but the great increase in area accounts for a large output of red corpuscles into the circulation.

There is also an increase of leucoblastic activity, a condition which is always associated with increased erythropoiesis. It is a curious fact, however, that the leucocytes in such a marrow do not necessarily appear in increased numbers in the peripheral circulation (see Pernicious Anæmia).

The spleen is enlarged, the pulp being hyperplastic and engorged

with blood, and infarctions are commonly noted. The liver and other organs, as well as the splanchnic vessels, show great congestion. In a few cases there have been arteriosclerosis and a moderate degree of cardiac hypertrophy. The blood-pressure is raised in typical cases, sometimes very considerably. This feature is apparently most marked in the rare cases in which there is no discoverable splenic enlargement.

As a result of the increased output of red (and sometimes white) corpuscles there is dilatation of vessels and capillaries and increased viscosity of the blood. Possibly symptoms may be masked for some time by an increased arterial blood-pressure, but by the time cases come under observation there is cyanosis, and sometimes thrombosis, hæmorrhage, or other local circulatory disorders.

Symptoms.—The onset is gradual. Lassitude and headache are perhaps the earliest symptoms. Dyspepsia, abdominal pain and tenderness associated with the enlarged spleen, thirst, and constipation are commonly present, but the condition is compatible in some cases with great physical and mental activity, and the absence of any but occasional symptoms. The liver may be slightly enlarged. The spleen always shows definite increase in size. The degree of enlargement may vary throughout the course of the disease.

Cyanosis is the rule, but it may be absent. The degree of blueness may be intensified by exposure to cold or by emotional conditions. The mucous membranes show the condition as well as the skin. Hæmorrhages from the various mucous surfaces have been recorded. Vascular engorgement may be seen with the ophthalmoscope. The blood-pressure is frequently above normal. Slight cutaneous pigmentation has occurred in a few cases. A white line may sometimes be induced by cutaneous irritation, and actual dermatographia has been noticed.

The condition of the urine varies. It is usually abundant, and may be clear, but often contains considerable quantities of urobilin. Albuminuria in varying degree may occur, and is often associated with the presence of tube-casts.

Blood Changes.—The red cells are increased in number, counts varying from 7 to 12 millions per c.mm. There is no great diminution in their size, so that counts much larger than 12 millions could hardly be obtained, although Koester has found 13,600,000 per c.mm. A few normoblasts have been noted in some of the cases. The hæmo-

globin value may reach 170 or 180 per cent., but the colour index is usually below 1. The white cells are practically always increased in number. Counts of 20,000 to 30,000 are common. The increase is accounted for by the polymorphonuclear cells, which frequently amount to more than 80 per cent. of the total. Myelocytes are sometimes seen. In Blumenthal's case there were 16,000 white cells per c.mm., with 36 per cent. myelocytes. No observations, so far as we know, have been made on the number of blood-plates. The specific gravity of the blood is increased. The viscosity is increased in proportion to the polycythæmia. No constant change in relation to coagulability has been noted. Cryoscopic examination has given negative results (Senator, Parkes Weber). The total volume of the blood, as tested by the carbon monoxide method of Haldane and Lorrain Smith, is considerably increased.

Course.—Many cases show little change, either for better or worse, for prolonged periods. Complications, apart from intercurrent affections, are not common, and are usually vascular disturbances. Erythromelalgia appears to be one of the most frequent. Hæmorrhages from mucous membranes may occur, and after the first shock is over, may improve the patient's condition by reducing the blood-count to more normal figures and lowering the blood-pressure.

Remissions for varying periods have been observed, and on the other hand sudden exacerbations of the cyanosis are not infrequent. The end is usually associated with one of these exacerbations, a vascular brain lesion, or an intercurrent affection.

Treatment.—The same careful régime as would be applicable to any vascular disorder is indicated in this condition. Stimulants, vaso-dilators, and those drugs (phenacetin, etc.) which have been known to cause polycythæmia are all to be avoided.

Drugs such as arsenic and iron, which are capable of stimulating the bone-marrow, are contra-indicated. Perhaps it would be worth while to take some steps to diminish the amount of iron in the food. A diet consisting largely of milk and rice preparations might therefore be tried.

Subjective symptoms have been benefited both by spontaneous and therapeutic bleeding. The blood-pressure would perhaps be the best guide to the advisability of venesection in any given case. A large number of drugs have been tried. A moderate amount of success

has followed inunction of biniodide of mercury over the spleen, the administration of quinine, and the prolonged administration of thyroid gland or iodothyrin.

Röntgen rays applied over the spleen and long bones have given inconsistent results. No benefit is to be expected from splenectomy.

Literature

Parkes Weber (*Quart. Journ. of Med.*, ii. 1908) and Watson-Wemyss (*Edin. Med. Journ.*, February 1911) give critical reviews, with full references to date.

Methæmoglobinæmia

Etiology.—This condition is caused either by the absorption of nitrites from the intestine in cases of diarrhœa, or by drug poisoning. The most common drug to cause cyanosis is acetanilide, which forms the basis of most "headache powders" in the market. Phenacetin, sulphonal, trional, veronal, potassium chlorate, and the nitrites may produce the same effect. Workers in these drugs and also in aniline dyes are not uncommonly affected.

Symptoms.—In acute cases there may be severe dyspnœa with a certain degree of heart failure; in more chronic cases headache and prostration may be the only symptoms beyond the cyanosis; in the intestinal (nitrite) cases there is diarrhœa. Spectroscopic examination of the blood shows a dark band in the red near the line C, which disappears, to be replaced by the band of reduced hæmoglobin, on the addition of a few drops of ammonium sulphide and the application of gentle heat.

Treatment.—In the acute cases due to drugs, emetics or lavage of the stomach may be required. The patient should have plenty of fresh air, and must be kept warm. Cardiac stimulants may be required. In the chronic cases the drug must be stopped; in the intestinal cases the methæmoglobinæmia will clear up within forty-eight hours on a purely milk diet, but the symptoms return within four hours after a full meal. It is important that diarrhœa should not be treated with subnitrate of bismuth, since certain intestinal bacteria may change nitrates into nitrites. Fatal cases were reported when this drug was in use in connection with X-ray diagnosis. Idiosyncrasy may, of course, play a part in them. The methæmoglobinuria disappears as the enteritis is cured.

Microbic Cyanosis

Under this name Gibson and Douglas [1] recorded the case of a married lady suffering from headaches, giddiness, and a tendency to faintness, with cyanosis. Red cells, 3,360,000; Hb 70 per cent.; leucocytes, 10,296. Methæmoglobin was found in the blood. Nitrites were found in the blood, but only in traces in the fæces. An organism, either B. coli or a closely allied bacillus, was grown from the blood. The suggestion was made that an infection of the blood from the bowel had occurred, and that a hæmatogenous formation of nitrites was keeping a varying amount of hæmoglobin in a condition of methæmoglobin, thus leading to false cyanosis. Improvement followed a course of intestinal antiseptics.

Sulphhæmoglobinæmia

Etiology and Pathology.—This condition results from the hyperformation or hyperabsorption of sulphuretted hydrogen, or from the presence in the blood of an abnormal reducing agent acting with a small trace of H_2S. Mackenzie Wallis [2] has studied five cases and found that sulphhæmoglobin partially replaces the oxyhæmoglobin of the blood and is present in the red corpuscles and not in the serum. The serum contained a strong reducing substance, possibly of the nature of a hydroxylamine, capable of producing reduction of the oxyhæmoglobin. This is an essential and primary stage in the production of sulphhæmoglobin.

A nitrite-producing organism was found in the saliva of all the patients, and it appeared to be capable of evolving the reducing substance.

Symptoms.—The symptoms are similar to those of chronic methæmoglobinæmia, from which the condition is distinguished by the spectroscope. The blood shows a dark band in the red. The band persists after warming the blood with ammonium sulphide, and may be intensified by the addition of a reducing agent such as phenylhydrazine.

The blood does not show the temporary improvement which occurs in methæmoglobinæmia when a milk diet is taken. West and Clarke [3] have described a case with 5,050,000 red cells per c.mm., Hb

[1] *Lancet*, 14th July 1906.

[2] *Quart. Journ. of Med.*, vii. 1913, p. 73.

[3] *Lancet*, 2nd February 1907. See also Clarke, *Med. Record*, 24th July 1909.

115 per cent. The blood gave spectra of oxyhæmoglobin and sulphhæmoglobin. H_2S was not found free in the patient's blood, but it was determined experimentally that the amount of H_2S required to cause an appreciable change in the blood-pigment at body temperature was far below that which could be detected by chemical means.

Treatment.—Treatment is unsatisfactory. If constipation or gastro-intestinal symptoms are present they should be dealt with, but it is open to question whether the intestine plays any direct part in the production of the condition. Wallis successfully treated one of his cases with an autogenous vaccine made from the nitroso-bacillus in the saliva. Similar treatment in another case failed.

Hæmochromatosis

This rare condition is associated with bronzing of the skin, due to a deposition of hæmofuscin. Part of the pigment contains iron, but in a more firmly combined condition than in hæmosiderin. There is degeneration of the cells of the liver, pancreas, and other organs, and cirrhotic changes due either to the pigment or to a hypothetical toxin causing the condition. The late stages of the disease may be associated with diabetes (*diabéte bronzè* of French writers).

Literature

Beattie, *Journ. of Path. and Bact.*, 1903. Roberts, *Brit. Med. Journ.*, 11th November 1911. Potter and Milne, *Amer. Journ. of Med. Science*, 1912, p. 46.

Lipæmia

This is a rare condition occurring in the course of diabetes mellitus. It usually affects young adults. The source of the fat in the blood is most probably the glucose. The condition is associated with acidosis. The symptoms of diabetes do not appear to be much modified by the presence of the lipæmia. The melting-point of the fat is below the body temperature, and when cooled the fatty particles are very small. The condition is diagnosed by the examination of blood-films. The red corpuscles do not readily form rouleaux, and they are somewhat cloudy in appearance. In one of Fraser's cases there was a leucocytosis of 23,000. In the plasma are numerous particles, highly refractile and showing Brownian movement. They may be found also in some of the large lymphocytes. These particles can, as a rule, be stained with osmic acid

or sudan. Hale White, however, reports a case of diabetes in which there was a granular precipitate in the blood plasma. This did not give the ordinary reactions of fat, but appeared to be a protein precipitated by the presence of a fatty substance, probably an ester of cholesterin with one or more of the higher fatty acids.

Cases can also be distinguished by the remarkably white appearance presented by the retinal vessels. In one of Fraser's cases the percentage of fat in the blood amounted to 12, in another to 16.

Treatment.—Fraser states that he has seen the disappearance of fatty droplets from the blood in one case of diabetes under the influence of alkaline treatment. He recommends the frequent examination of the urine of diabetics for the presence of β-oxybutyric acid, and of the blood for fat, especially in the case of young subjects. The finding of either is an indication for treatment by a liberal administration of alkalies.

Literature

Fischer, *Virchow's Archiv*, Bd. clxxii. Fraser, *Scottish Med. Journ.*, September 1903. Hale White, *Lancet*, 10th October 1903. Turney and Dudgeon, *Journ. of Path. and Bact.*, xi. 1906.

CHAPTER XX

LEUCOCYTHÆMIA—LEUKÆMIA

Definition.—A disease characterised by a persistent increase of white cells in the blood.

Classification. — The disease occurs in different forms. When Ehrlich first introduced methods of differential staining of leucocyte granules he made a sharp distinction between the lymphocytes or non-granular cells, on the one hand, and the neutrophil, eosinophil, and basophil leucocytes on the other. He regarded all the lymphocytes as being derived from the lymphatic glands and lymphoid tissues and the granular cells as taking origin in the bone-marrow.

He therefore divided leucocythæmia into lymphatic and medullary, considering the first was a disease of the lymphatic glands and the latter a disease affecting the bone marrow. Subsequent research has altered this conception in several directions.

It is now known that all the leucocytes are derived from a common ancestor, the primitive leucocyte, which so closely resembles the large lymphocyte of the blood as to be indistinguishable from it. It has been pointed out by Pappenheim, Walz, and ourselves that cases of lymphatic leukæmia may occur without any glandular enlargement. In these cases the marrow showed marked lymphoid hyperplasia. It therefore became necessary to revise our views, and it was recognised that while there was a distinction between lymphatic leukæmia and myelocythæmia, the former, as well as the latter, might be a disease of the bone-marrow.

But a new difficulty has arisen. Naegeli has made a division of the large lymphocytes into large lymphocytes proper and myeloblasts (p. 68). The latter acquire granules and become pro-myelocytes, then myelocytes, then polymorphs.

These myeloblasts can only be distinguished by special modern methods of staining, but the distinction finds confirmation in the oxydase reaction. Myeloblasts give a positive reaction, lymphocytes do not. But here matters are complicated by Dunn's observation that

myeloblasts, early enough in their life history, fail to give a positive oxydase reaction. This suggests the obvious inference that lymphocytes may acquire the oxydase ferment and become myeloblasts; in other words, that the myeloblasts of the bone-marrow have arisen from lymphocytes. Time and subsequent research will doubtless arrange these findings in true perspective, and we disclaim any desire to minimise their interest or importance from the cytological standpoint. We wish, however, to point out that too great insistence on the hæmatological minutiæ may bring nothing but confusion to the mind of the clinician. Many cases of leukæmia in which the preponderating cells have been thought to be myeloblasts have been reported as instances of *myeloid* leukæmia.

Now the great majority of leukæmias with non-granular cells run an acute course and have the same general symptoms, whether the preponderating cells are myeloblasts or lymphocytes.

A week's observation will readily determine whether an individual case is to fall into the comparatively rare chronic type of non-granular leukæmia.

The great majority of cases of leukæmia with a preponderance of granular cells run a chronic course with different symptoms, and examples of granular-cell leucocythæmia which run an acute course are excessively rare.

We would therefore plead, if on no other ground than as a concession to the clinician who may have little knowledge of cytology, that the original classification of Ehrlich be maintained and that the term *myeloid* or medullary leukæmia be meantime restricted to these cases in which the preponderating cells are definitely granular—myelocytes and polymorphs—and that the cases in which the preponderating cells are non-granular be termed lymphatic whether the cells are lymphocytes or myeloblasts in the histological sense. The "mixed" cases might be recorded as such.

In our description we propose to follow this plan and the following classification will be adopted:—

1. Lymphatic (non-granular) leukæmia (lymphocythæmia; lymphæmia)—(*a*) acute, (*b*) chronic. 2. Myelogenous (granular) leukæmia (myelocythæmia; spleno-medullary leucocythæmia; myelæmia)—(*a*) chronic, (*b*) acute. 3. Mixed forms. 4. Chloroma. The order of frequency of these forms is, in our experience, acute lymphocythæmia, chronic myelocythæmia, chronic lymphocythæmia, and acute myelocythæmia. Mixed forms and chloroma are about equally rare.

1. Lymphatic Leucocythæmia

Etiology.—The disease is by far most common in children, adolescents, and young adults. It may, however, occur at any age. We have seen an acute case in a man aged sixty-one, another in a man of seventy-two, and Bramwell records a case of chronic type beginning at the age of seventy-eight. The disease is much more frequent in males than females.

A host of possible causal factors has been suggested, but none of them have been sufficiently common to amount to more than coincidence. Hæmorrhage has frequently been alleged to be a cause of the disease, but it is much more likely to have been an early symptom.

Morbid Anatomy and Histology.—The essential feature of the disease is an overproduction of lymphocytes which pass into the blood-stream, infiltrate the various tissues and organs, except the central nervous system, and lead to interference with nutrition. Hæmorrhages are very common.

Alimentary Canal.—There is sometimes enlargement of the tonsils. There is an increase of lymphocytes in the walls of the stomach and intestine, and in some cases their amount is so great as to cause separation of the tubules.

Heart.—There is gross lymphocytic infiltration of the heart in about half of the cases. An extraordinary degree of separation of the muscular fibres sometimes occurs. There is often fatty degeneration of the heart muscle.

Liver.—The liver may be slightly enlarged. It is often the seat of very great infiltration. There may be masses of lymphocytes visible to the naked eye under the capsule and in the portal tracts. The lymphocyte infiltration begins in the portal tracts and at the periphery of the lobules, but may extend up the rows of liver cells, in some cases right up to the intralobular vein. In extreme cases the liver may be represented by small islands of hepatic cells lying between masses of invading lymphocytes. Cells other than lymphocytes are uncommon in those areas, but sometimes cells resembling the giant cells of bone-marrow may be found, and large phagocytic cells ingesting lymphocytes and red cells are sometimes present.

The liver cells may look healthy but are often fatty. They always contain a large amount of granular pigment, which gives the reaction for free iron in the majority of cases. The pigment is chiefly found at

the periphery of the lobules, and in the acute cases is sometimes as abundant as in pernicious anæmia or any other condition.

Kidneys.—The kidneys are usually enlarged and show massive infiltration leading to alteration of structure. There are often hæmorrhages which may give rise to a remarkable "piebald" appearance. The hæmorrhages often destroy areas of cortical substance. Massive lymphocyte infiltration is the rule; it may lead in some cases to atrophy and fibrosis of some of the glomeruli. Large phagocytes are sometimes to be seen ingesting lymphocytes in the infiltrated areas.

Spleen.—The spleen is always enlarged, but in the very acute cases the enlargement may be very slight. The Malpighian bodies are generally atrophied, rarely normal. We have never seen them enlarged. The pulp is generally packed with lymphocytes, and among them there are large phagocytic cells ingesting them. The endothelial cells of the sinuses are exceedingly prominent and may be cubical or columnar in shape. There is a considerable number of giant cells of bone-marrow type. There is nearly always a fair amount of pigment, which often gives the iron reaction. In a few cases there is a considerable fibrosis of the pulp.

Lymphatic Glands.—In the great majority of cases the lymphatic glands are enlarged, but this is not an absolute rule. We commonly find that the more chronic the course of the disease the greater size do the glands attain and the more numerous are the glands affected. In chronic cases nearly every gland in the body may be enlarged, and many of them may be as big as a large walnut.

The enlarged glands show packing with lymphocytes to such an extent that all distinction between cortex and medulla is lost, and sections show a remarkable uniformity of structure. The blood-vessels are large and no longer show the typical arrangement. Germ centres are not found. There are often phagocytes and sometimes giant cells in the pulp. The lymphocytes sometimes show a remarkable condition of branching or karyorrhexis of the nucleus.

Hæmolymph glands are generally unrecognisable as such owing to the packing of the sinuses with lymphocytes. Normoblasts are sometimes to be seen in the sinuses, and phagocytosis of lymphocytes and red cells, with the subsequent pigmentary changes, is not uncommon. The thymus is not enlarged and usually shows little change.

Bone-Marrow.—The yellow marrow is always replaced to a large extent or entirely by red marrow. The fat has in many cases completely disappeared, and sections show an even distribution of lympho-

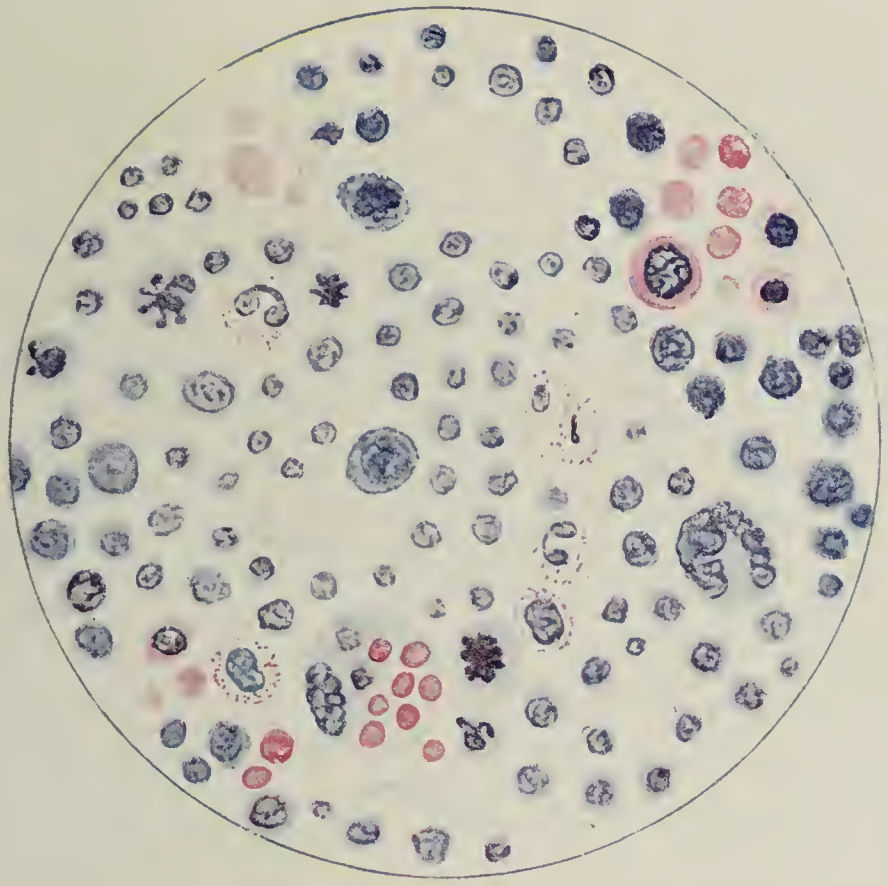


FIG. 1.—SECTION OF BONE-MARROW FROM CASE OF ACUTE LYMPHATIC LEUKÆMIA (Eosine and Methylene Blue).

Shows great proliferation of lymphocytes, mostly small. Some show curious branching or karyorrhectic nuclei, others show mitosis.
There are two normoblasts and two megaloblasts and very few granular leucocytes.
A phagocytic giant cell contains seven erythrocytes and two lymphocytes.

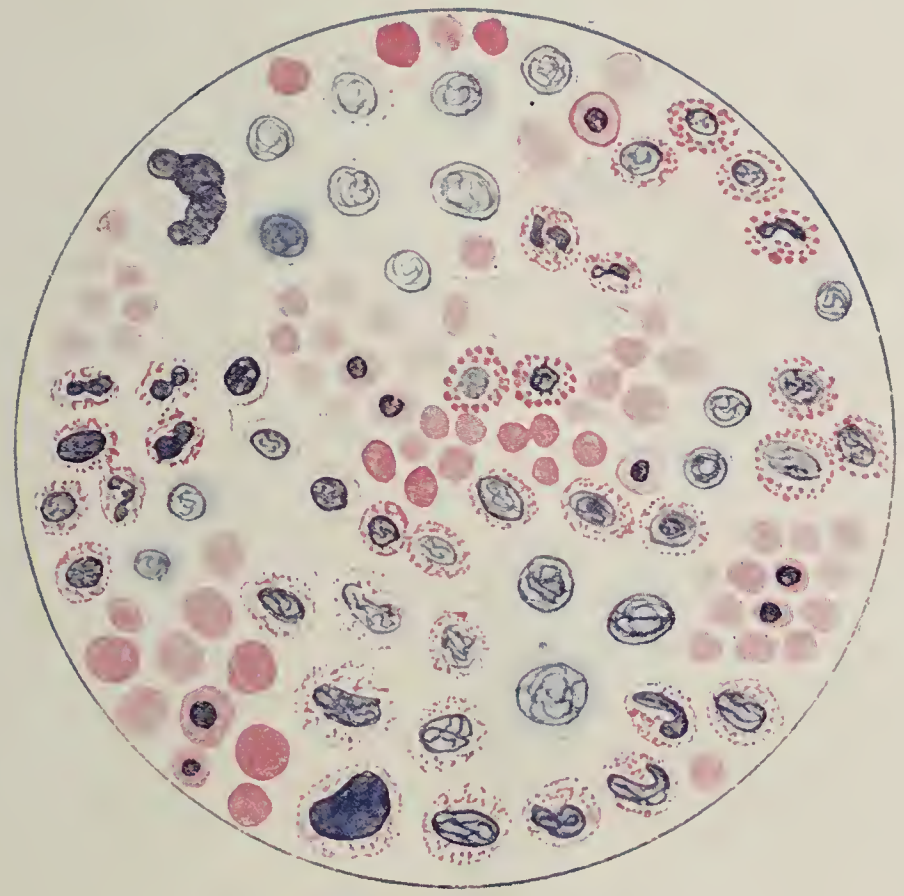


FIG. 2.—SECTION OF BONE-MARROW FROM CASE OF MYELOCYTHÆMIA.

Shows numerous neutrophil and eosinophil myelocytes and a large number of lymphocytes. Normoblasts are fairly numerous.

A. G., *fecit.*

cytes with a fair number of red corpuscles. The lymphocytes are both large and small, but in most cases one or other variety seems to preponderate in overwhelming numbers.

Erythrocytes are generally the next most numerous type of cell and then myelocytes, but their proportions to the lymphocytes are very small. Normoblasts are present in small numbers and megaloblasts are sometimes seen. Giant cells are scanty and degenerated. Iron-containing pigment is often present. Phagocytosis is usually seen.

Relation of the Morbid Changes to Pathology.—The occasional absence of infiltration from the alimentary tract and its moderate amount when present appears to exclude the alimentary canal from any causal connection with the disease, and we do not find any special tendency to alimentary disorder in the previous history.

The degenerative changes found in the liver are not peculiar to this disease. The large amount of iron pigment often found is accounted for by storage of iron derived (1) from normal corpuscles and not again utilised by an inefficient marrow; (2) from hæmorrhages; and (3) from specially vulnerable corpuscles developed late in the disease. The evidence afforded by the changes in the spleen suggests that the accumulation of lymphocytes in the pulp is due to a passive accumulation there rather than an increased production. On the other hand, there is strong evidence of destruction of lymphocytes by the phagocytic action of large cells in the pulp and by endothelial cells proliferated from the walls of the sinuses. So many cases have now been published and seen by ourselves in which the lymphatic glands were not affected that we believe that they have no primary causal relation to the disease.

The bone-marrow in all cases shows proliferation of lymphocytes to such an extent as almost entirely to replace the other varieties of cells. This change may exist without glandular enlargement, consequently we regard the bone-marrow as the primary and essential seat of the disease.

It may be noted that patients do not die of the increase of leucocytes, but rather of the anæmia which coexists or of intercurrent diseases (except in so far as hæmorrhages may be due to thrombosis of vessels by masses of leucocytes). The anæmia is more marked in proportion as the condition is more acute, because the available space for erythrocyte production is rapidly taken up by lymphocytes, and the spread in the fatty marrow is a spread of lymphocytes

and not of erythroblasts. As a result of this, when the normal red corpuscles in the blood die out in the ordinary course their place will not be taken by new ones of normal type, but by the badly formed red corpuscles which always appear when there is an extra demand for these corpuscles and an insufficient supply, and ultimately by normoblasts and even megaloblasts. A further cause of anæmia is the ingestion of red cells by the phagocytes which are so numerous in this condition and by endothelial cells. The iron derived from the hæmoglobin of the destroyed corpuscles is either retained in the phagocytes and endothelial cells in the various organs in which the process of phagocytosis goes on, or, in the case of red cells which are destroyed in the blood-stream itself, is taken up by the liver cells and retained there, partly because the functions of the liver itself are interfered with by the disease, partly because there is little or no demand for it for the production of new red cells. In the chronic cases the anæmia is never so severe as in the acute cases, apparently because the change in the marrow is slower, so that erythroblastic proliferation can proceed *pari passu* with lymphocyte proliferation; and in the extremely chronic cases it seems probable that supplemental erythrocyte formation takes place in the liver and spleen, as indicated by the presence of normoblasts and giant cells. A long time, however, must elapse before this is brought about.

It seems to us that these considerations are sufficient to account for the anæmia without the operation of a hypothetical toxic condition.

The same applies to the polymorphs. The frequency with which cases of lymphatic leukæmia die of pneumonia and other intercurrent diseases may be explained by the fact that the granular cells which respond defensively to infection by the pneumococcus, for instance, are very few in number in the marrow, having been crowded out by lymphocytes, and that the patient's resistance is hampered by the small number of polymorphs which he can muster against the infection. As bearing this out, it may be quoted that we have found some evidence of supplemental granulocyte formation in the spleen and other organs—myelocytes and eosinophil myelocytes were found more frequently than normal.

While patients do not die directly of the leucocyte increase, there can be no doubt that the enormous deposits and infiltrations in organs must interfere greatly with their functions. This is more prominent in some organs than in others. For example, the alimentary tube in our cases seems to have suffered comparatively little in this way, the

heart also slightly, while tonsils, lungs, pancreas, thyroid, suprarenal, general muscular system, etc., were little affected. On the other hand, apart from the profound alteration in the true hæmopoietic organs, the kidney is almost always affected, though to a very variable extent, and though the secreting tubules do not suffer to anything like the extent that they do in pernicious anæmia. The liver is the organ which is most profoundly affected, and all its functions must be greatly interfered with by the pressure on its secreting cells which the infiltration causes.

Pathology.—Much interesting speculation has centred round the question of the cause of the leukæmic change in the bone-marrow. The chief points may be briefly recapitulated. The possibilities are that the proliferation may be due to some chemiotactic influence, that it may be of the nature of tumour growth, or that it may be due to some disturbance of the balance of nutrition which either encourages the overgrowth of lymphocytes or removes some restraint on their development. In the present state of our knowledge the two latter possibilities may be taken as one, and the question may be asked whether the condition is simply a useless overgrowth of lymphocytes, for useless overgrowth is practically synonymous with tumour in the broad sense in its results, though the process may be different in origin.

As regards chemiotaxis, it may be taken that they are lymphocytes in the normal bone-marrow, and that certain toxins (whooping-cough, smallpox) may cause a chemiotactic increase of lymphocytes in the blood.

On the other hand, the following reasons against the chemiotactic theory may be adduced :—

1. No organismal or other toxin has been found constantly associated with the disease.

2. The ordinary channels of entry of infective disease—the alimentary canal and the lungs—show only a slight degree of lymphocyte infiltration.

3. The function of all the organs in which infiltration takes place is greatly interfered with. The chemiotaxis known to be associated with other forms of disease never reaches this extraordinary degree.

4. Lymphocyte infiltration occurs in organs and tissues in which it seems impossible that it could appear in response to any known chemiotactic stimulus. We may instance the fatty tissue, the heart muscle, the pancreas, the thyroid, etc.

5. The more chronic the process the greater the infiltration and the

number of lymphocytes in the blood tend to be. This is just the reverse of the usual rule in the case of response to known chemiotactic stimuli. Moreover, the actual number of lymphocytes in the blood in some lymphatic leukæmias is much greater than ever occurs in infections.

6. It is difficult to believe that the large labile lymphocytes which are found in many cases of leukæmia could be of any service in a chemiotactic sense. Infections, however severe or prolonged, are associated with a fairly normal type of cell which never shows the extravagance in size or the extent of degeneration which is common in lymphatic leukæmia.

7. In chronic lymphatic leukæmia symptoms are sometimes ameliorated by treatment with X-rays, although a large number of lymphocytes are destroyed. If they were there for any useful purpose their destruction should not lead to improvement.

8. It is difficult to conceive of any organised chemiotactic influence lasting for years as in the chronic cases and keeping up and increasing the alterations in the blood and throughout the body.

The following points seem to us to be strongly in favour of the view that we have to deal with a useless proliferation of lymphocytes:—

(*a*) It is is impossible to distinguish histologically and, except for the presence of the green tumours, even clinically between lymphatic leukæmia and chloroma. In the latter disease there is a formation of true multiple tumours which may erode bone and other tissues. Further, it must not be forgotten that in lymphatic and myeloid leukæmia there may be swellings on the gums, the skin, and even the alimentary canal, which may be considered analogous to the tumours of chloroma.

(*b*) The nuclei of many of the lymphocytes in a fluid mount containing a nuclear stain are stained at once, while the polymorphs remain colourless. Normal lymphocytes do not show the same early staining. The early colouring is evidence of the effete character of the cells. The great amount of phagocytosis of lymphocytes in the organs and tissues points in the same direction.

(*c*) Lymphatic leukæmia is invariably fatal, whether in the acute or chronic form. This cannot be said of any infection.

The only real difficulty in the way of the view that lymphæmia is analogous to tumour growth is the widespread growth of lymphocytic marrow in so many, if not all, of the bones. It is a little difficult to conceive of such a widespread change beginning in a single cell or group of cells as a tumour does. It seems more probable that the

disease is caused primarily by some disturbance in metabolism, of such a kind that the growth of lymphocytes is either encouraged or perhaps, more probably, is not restrained as it is in the normal organism.

While we conclude that the bone-marrow is the primary and essential starting-point of the disease, we have still to consider whether the infiltration of organs and tissues is entirely due to packing with lymphocytes derived from the marrow and deposited by the blood. The outstanding fact regarding this infiltration is its irregular and exceedingly capricious incidence both as regards locality and amount. In the lymph glands, germ centres, the normal breeding-places of lymphocytes, are inconspicuous or absent. In the spleen the Malpighian corpuscles are small and sometimes fibrous, and the Peyer's patches and other masses of lymphoid tissue throughout the body are inactive. We do not consider that there is a general hyperplasia throughout the body in addition to the bone-marrow lesion. The lymphoid tissues are invaded, and the invading lymphocytes may and do undergo mitosis and give rise to a (metaplastic) increase. This is at the expense of the local lymphoid tissue, as is evidenced by its atrophy.

Pappenheim and Hirschfeld[1] have recorded a case of acute lymphatic leukæmia in which there was the usual appearance of the marrow, but the lymphatic glands showed hyperplasia of the follicles. The Malpighian bodies in the spleen were greatly hypertrophied and to some extent confluent. The liver showed circumscribed islands of small lymphocytes in the fibrous tissue rather than the usual diffuse change. They seek to separate lymphatic leukæmia into two types—myeloplastic and lymphoplastic. In the course of a large experience of the disease we have never seen a case of the lymphadenoid or lymphoplastic type. Granting its existence as a change secondary to the bone-marrow disease, it does not much alter the conception of the disease we have set out. In our opinion all the cases which show the typical blood changes of lymphatic leukæmia have their origin in the bone-marrow, but it must be admitted that the view that the disease is the expression of a general lymphatic hyperplasia is widely held. There is no essential distinction as regards their pathology between the acute and chronic cases.

Symptoms.—(a) *Acute Lymphatic Leukæmia.*—The onset may be insidious, but more commonly the initial symptoms are severe. A slight enlargement of a small group of glands may be noticed, usually

[1] *Folia Hæmatologica*, v. 1908.

about the neck. This may remain unaltered, or the swelling may rapidly increase and be followed by enlargement of other groups. Extravasations of blood into the skin may call attention to the condition. Hæmorrhage from mucous membranes is a common initial symptom, especially from the nose and the gums. Some cases begin as an acute febrile attack without very definite symptoms and without enlargement of glands. There may be pain in the long bones or over the sternum. There may be little change in the clinical picture from first to last. There is, of course, increasing weakness, and there is always progressive anæmia, with breathlessness, faintness, and dyspnœa.

When the disease is fully established in a typical case the temperature is about 102° F.; the face has a pale waxy appearance. The mucous membranes are exceedingly pale. There may be no enlargement of glands, but occasionally there may be groups of enlarged glands in the submaxillary region, neck, axillæ, groins, and popliteal spaces, while even the epitrochlear and others not so commonly noticed may be involved. These widespread enlargements are more common in the less acute cases. The tonsils may be enlarged. The abdomen may be prominent from enlargement of mesenteric and retroperitoneal glands. The spleen is always enlarged, but the extent of the enlargement varies very greatly. As a rule, the more acute the case the less enlargement will there be. The liver also may show a moderate increase in size. There may be nausea and vomiting, sometimes diarrhœa, but constipation is more common.

Perhaps the most distressing of all the symptoms are the hæmorrhages. Attacks of epistaxis are common. Bleeding from the gums is another very common feature. A slight persistent oozing from different points in the alveolar margin of the gums takes place. Pieces of clot get entangled in the teeth. Should the bleeding stop, the attendants are content to leave well alone rather than attempt their removal, so that the mouth becomes very foul, the tongue being dry and covered with sordes. Bleeding may be arrested at one point only to break out at another, and if perchance the gums stop bleeding for a time, the interval is often occupied by epistaxis.

The nose is often blocked, so that patients breathe through the mouth. A diphtheritic membrane may form on the gums or cheeks. There may be local necroses and ulceration. The teeth loosen, and the condition of the mouth resembles that seen in scurvy. Hæmatemesis and hæmaturia are less common forms of hæmorrhage. Bleeding from any mucous membrane may take place. Bleeding may cease some days

before death, and occasionally deafness may come on from hæmorrhage into the inner ear. In one of our cases blindness in both eyes occurred from hæmorrhage into the vitreous.

Purpuric spots are common. There may be difficulty in getting bleeding from a slight skin puncture to stop. A hypodermic injection may lead to the formation of a hæmatoma, and a slight knock may be followed by a large ecchymosis. Hæmorrhagic retinitis sometimes occurs, and cerebral hæmorrhage is an occasional termination. The urine shows no constant changes beyond those associated with fever. There is often an increase in the output of uric acid, and albuminuria may appear. Paralysis of cranial nerves from lymphoid infiltration or growth about their sheaths is sometimes met with.

The rapid anæmia causes the usual dilatation of the heart with systolic murmurs, and œdema of the feet and legs often appears towards the end. The pulse is rapid, of poor force, and low pressure. Mental symptoms are not uncommon. The patient may either become quiet, stupid and comatose, may merely wander in his talk, or may be talkatively delirious. He is too weak to be violent. The end may be hastened by intercurrent diseases, especially by pneumonia and pleurisy. In one case the occurrence of an extensive dry pneumococcal pleurisy was the first thing which drew attention to the patient's condition.

(b) *Chronic Lymphatic Leukæmia.*—This form is much less common than acute lymphæmia. The onset is always insidious. As a rule enlargement of groups of glands takes place and increases, sometimes to an enormous extent. Almost every gland in the body may be increased in size, and individual glands may be as large as hens' eggs. Cases without glandular enlargement, however, have occurred. The spleen enlarges and reaches an enormous size. The liver, too, increases in size. For long there may be no other symptoms. The functions of various organs may be interfered with from the lymphatic invasion. Great general weakness and anæmia eventually supervene, and the patient becomes breathless and dyspnœic. Lymphomata sometimes develop in the skin. They may be small tubercles, or may be as large as a bean. The larger nodules are most common on the face. The tumours grow very slowly and have little tendency to break down. Bence Jones' proteinuria has been recorded in a few cases.[1]

Many patients go about their usual work apparently little disturbed in spite of high leucocyte counts, great glandular and splenic enlargement, and anæmia, until the final breakdown comes which carries them

[1] Boggs and Guthrie, *Johns Hopkins Hosp. Bulletin*, December 1913.

off in a few weeks. The final stage may be one of anæmia and cachexia, but many cases end up with the symptoms usually associated with an acute attack.

Other cases die from the effects of pressure by the enlarged glands, and sometimes the end is brought about by an intercurrent affection.

In rare cases there is remission with or without treatment. These are so uncommon that the following case is worth detailing :—The patient was a man of nearly seventy, whom we saw for the first time in November 1910. He had been in excellent health till the end of July in that year; then he became gradually paler and progressively weaker. Two counts made a fortnight before we saw him gave the same result—reds, 2,500,000; hæmoglobin, 50 per cent.; colour index, 1; whites, 54,000, over 90 per cent. of which were lymphocytes. There were some nucleated reds in the first set of films (after a journey), not in the second. No lymph glands were enlarged, liver was normal in size, spleen just palpable at the edge of the ribs. There had been no hæmorrhage. Our count was reds, 1,500,000; hæmoglobin, 33; colour index, 1·1; whites, 135,000; lymphocytes, over 90 per cent.; no nucleated reds. We feared that he would go steadily downhill, and as he wished to return to his home in the country, allowed him to do so, with directions to take arsenic and naphthalene tetrachloride. He improved steadily, but gave up the arsenic, of which he had never taken more than 5 ♏ t.i.d., in April 1911, as he had a very severe herpes of the right side of the head and neck and inside the mouth. The other drug was continued steadily. We saw him again in October 1911, when he looked practically well, and complained of nothing except some neuralgia persisting after the herpes. His heart sounds were normal; the spleen was normal in size; no glands could be felt anywhere. The count was reds, 4,240,000; hæmoglobin, 75 per cent.; colour index, 0·9; whites, 7300, of which lymphocytes were 75 per cent., polymorphs 25 per cent. The lymphocytes were all either small or medium in size; there were none of the "dropsical" cells which were present before.

The Blood Changes.—In a typical case the blood is pale and watery. Coagulation time *in vitro* is apparently not diminished. There is always anæmia. In the acute cases, and particularly in the hæmorrhagic forms, the anæmia may be extreme. In one of our cases the red cells fell from 4,000,000 to 660,000 per c.mm. in ten days. The red cells show the ordinary features found in secondary anæmia, but in

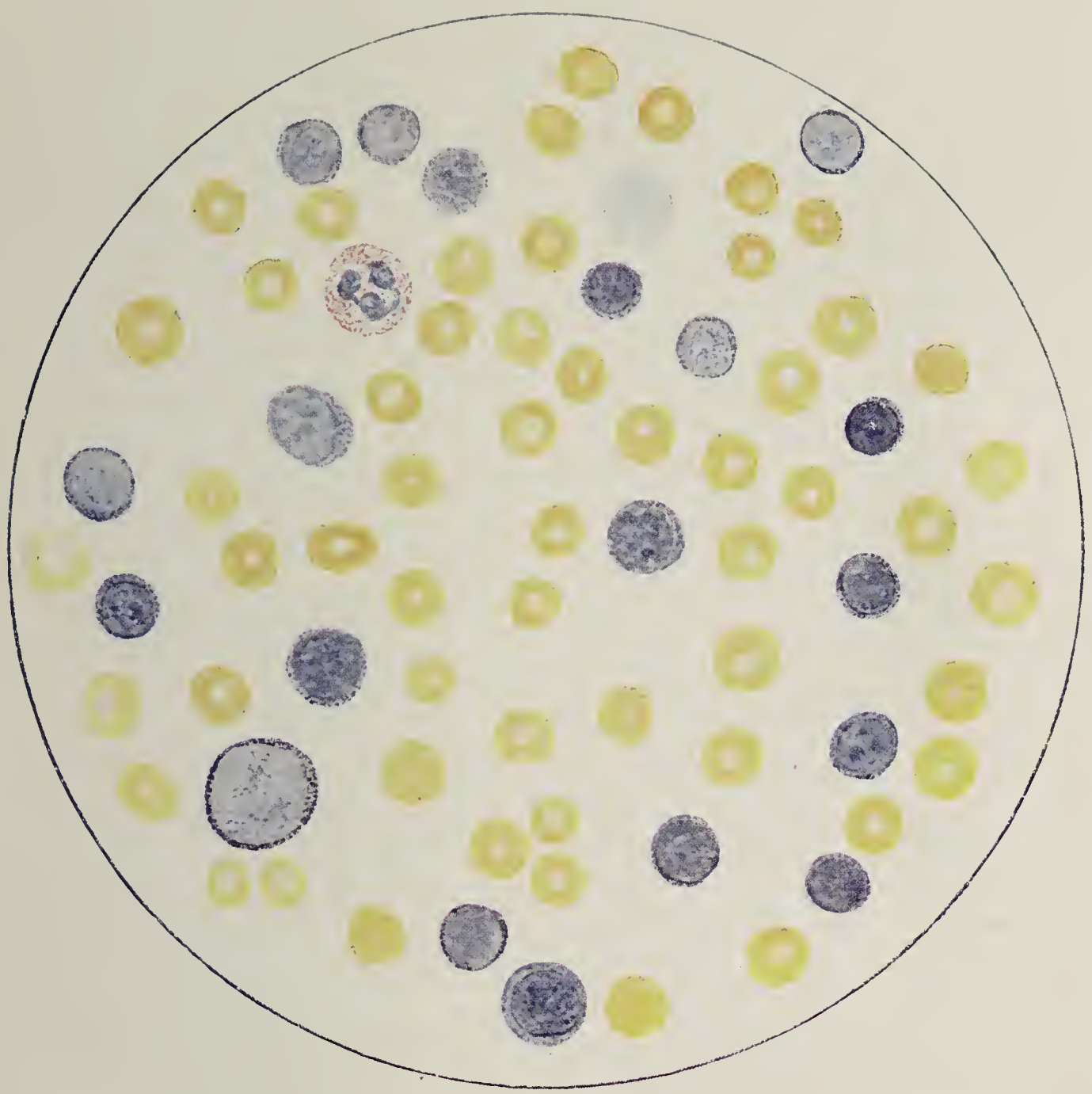


PLATE X.—ACUTE LYMPHATIC LEUKÆMIA (Jenner's Stain).

A. G., *fecit.*

most advanced cases there is a disturbance of the marrow leading to the output of numerous nucleated red cells into the circulation.

Normoblasts are sometimes found in large numbers, even at an early stage. There may be 500 per c.mm. when the number of red cells has fallen to 4,000,000. In the later stages megaloblasts are also present in large numbers, especially in young subjects. The hæmoglobin is of course also greatly diminished, and the colour index is low in the early stages of the disease. As the anæmia becomes greater it may rise again, reaching unity or even exceeding it. This is always associated with a megaloblastic blood-picture.

White Cells.—The leucocyte count is almost always increased. The numbers reached in the chronic cases are much higher than those found in the acute cases. In chronic lymphæmia counts of over 500,000 are not unknown, but in the acute cases the numbers seldom exceed 150,000 per c.mm.

Much lower counts, however, are the rule in both. Cabot puts the average in the chronic cases at 100,000. We should be inclined to make it rather higher, say, 150,000. It is difficult to name an average for the acute cases, for many of the "acute" cases published have really been merely the acute terminations of chronic cases, and in them the count is naturally high. Any "acute" case in literature which has shown *marked* enlargement of the spleen should be regarded with suspicion. In the really acute cases the count is often surprisingly low. We have several times made the diagnosis with counts as low as 10,000, and once with a count of 6800, and have seen these cases die with counts of 17,500, 19,000, 20,000, and 25,000. In one remarkable case, which was complicated with tuberculosis, the count remained at about 4000 for several weeks. All these cases showed over 90 per cent. of lymphocytes, usually about 98 per cent.

The increased white cell count is entirely due to an increase in lymphocytes, either large or small. It has been thought that the type of the disease could be predicted from the kind of lymphocyte preponderating in the blood. Large lymphocytes were supposed to be characteristic of acute cases and small lymphocytes of chronic. From the subjoined table, compiled from a set of cases occurring in a given time, and not otherwise selected, it will be seen that there is absolutely no general rule in either acute or chronic cases. In either class of case the large or small cells may be in excess; they may be equal in amount, or there may be so many transitional forms between the two that it may be impossible to make an accurate differential count. The only point

about the acute cases is that they sometimes seem to lead to extravagance in one direction or another. In no chronic case have we seen such large dropsical cells nor such small cells as in some of the acute ones.

	Large.	Small.	Remarks.
Acute—			
M., æt. 13 . . .	...	...	Gradations so numerous that it was impossible to make accurate count. Most were fairly large.
M., „ 61 . . .	1	99	Unusually small lymphocytes.
M., „ 19 . . .	54	46	Many doubtful and many burst.
F., „ 15 . . .	22	35	43 per cent. intermediate.
M., „ 5 . . .	16	84	
M., „ 17 . . .	76	24	Many of large swollen and dropsical.
F., „ 6 . . .	98	2	„ „ even more marked.
M., „ 13 . . .	34	66	
M., „ 18 . . .	80	20	
Subacute—			
M., æt. 22 . . .	75	25	
M., „ 22 . . .	...	...	Impossible to distinguish, so many transitions.
M., „ 30 . . .	31	69	Many intermediate.
Chronic—			
M., æt. 70 . . .	31	69	„ „
F., „ 42 . . .	83	17	
M., „ 40 . . .	60	40	
M., „ 56 . . .	90	10	
M., „ 53 . . .	58	42	

The percentage of lymphocytes is usually over 90 and is not infrequently 99. Occasionally the lymphocytes (usually large) show marked vacuolation, usually in the cytoplasm, but sometimes in the nucleus also. The "dropsical" cells have already been referred to. They are more numerous in the acute cases, and vary greatly in number. In stained films they are large cells whose cell-body and nucleus are pale, and hardly take up any stain. The nucleus often seems to merge indefinitely into the cell-body. These cells are easily destroyed in the making of films, and nothing may be left of them but a pale irregular nucleus. They are obviously degenerated forms.

The actual number of polymorphs may be about normal but is often somewhat reduced. A few myelocytes are always present in the acute cases, in small numbers to begin with, but becoming more numerous.

Eosinophils are always diminished. In one case we saw a considerable increase in the number of basophils. Blood-plates are always diminished.

Diagnosis.—Judging from the large number of cases we have seen diagnosed for the first time in the post-mortem room, and the number of times we have seen cases wrongly diagnosed, we have no hesitation in saying that acute lymphatic leukæmia is a much more common condition than is generally supposed. The diagnosis is perfectly simple if the blood be examined. It may be impossible if the condition of the blood is unknown.

The important point to recognise is that the excess of leucocytes to begin with may not be very great; but if there be a definite excess, and the percentage of lymphocytes be over 85, there can be little doubt of the nature of the case. Stress is to be laid rather on the lymphocyte percentage than on the total count. We have seen a somewhat similar blood-picture in a few cases of tuberculosis, though never with quite so high a lymphocyte percentage, and if a real difficulty arose in this direction a tuberculin test might be applied. The possibility of the existence of a tuberculous nodule in a case of leukæmia must be remembered. The course of the two conditions is so vastly different that in any case the doubt would not be of long duration. In chronic lymphatic leukæmia the number of lymphocytes in the blood is so great that the diagnosis need never be in doubt.

Intercurrent affections may lower the total count, but the percentage of lymphocytes remains high. In the rarer cases in which a polymorph leucocytosis is superadded to the lymphocytosis the percentage of lymphocytes usually remains above 75. The same holds for remissions. Even though the count returns to normal the lymphocytes will remain at about 75 per cent.

Prognosis.—The disease is uniformly fatal. The chronic cases have a somewhat precarious expectation of a few years of life, but many are dead within twelve months. Remissions may, however, occur, with complete loss of symptoms, diminution of the enlarged spleen, liver and glands, normal red count and hæmoglobin, normal white count, but in our experience the lymphocyte percentage always remains high.

The acute cases vary considerably, but within narrow limits. Some cases die within two days of an initial hæmorrhage. Perhaps most commonly the duration of the disease after it has attracted attention

is from a fortnight to a month. A few cases live for from three to six months. Very rarely cases begin acutely and become chronic. Rupture of the spleen is a rare complication.

Serious symptoms are sudden onset, high temperature, hæmorrhages, and rapidly advancing anæmia. A falling leucocyte count does not necessarily indicate any amelioration in the patient's condition.

Treatment.—In acute lymphæmia the general treatment is that of any febrile condition. Special care is required to avoid any slight injury which might lead to bruising. The most urgent symptom is generally hæmorrhage, and sometimes the medical attendant may arrive at the end of his resources without being able to control it. Adrenalin does not seem to do much good. Although it is messy and leaves an ugly black clot, we have found the liquor ferri perchloridi fortior specially efficacious in controlling bleeding from the gums and anterior part of the nose.

No known drug has the slightest influence on the course of the disease. X-rays certainly do harm in the acute cases; they seem to exercise a toxic influence. The temperature rises, and the disease seems to run its course more rapidly when they are used.

The chronic cases should lead a healthy outdoor life as long as possible. Arsenic and X-rays should be tried as in chronic myelocythæmia, and are sometimes useful. In a recent chronic case symptomatic improvement coincided with the use of naphthalene tetrachloride in 5 to 10 grain doses.

Benzol administered in the form of 5 ♏ capsules, along with 5 ♏ of olive oil, has been given in doses up to 20 ♏ three times a day in a small number of cases, and a measure of improvement has followed in a few instances. In others no benefit has been obtained, and in one instance necrotic areas found in the liver after death were attributed to its administration.

Thorium X has also been tried, but its use has no very enthusiastic advocate.

CHAPTER XXI

LEUCOCYTHÆMIA—(*continued*)

2. Myelocythæmia

Etiology.—The disease may occur at almost any age, but it is very much more common between the ages of twenty and fifty than at any other time of life. A small number of cases have occurred in infancy, and a few congenital cases have been recorded (Chap. XXVII.). It is more frequent in males than females, the proportion being approximately two to one. Overwork, worry, unsuitable surroundings and bad food are among the factors which have been supposed to be causal. All such suggestions are mere conjecture.

Morbid Anatomy and Histology.—The general appearances are pretty much the same as those of lymphatic leukæmia. The alimentary canal seldom shows any gross lesion, and the microscopic changes are but slight. An increase of white cells in the submucosa is the main feature. Intestinal ulcers have been noticed in a few instances.

Liver.—The liver is considerably enlarged in a fair proportion of cases. This is mainly due to a packing of the portal spaces and hepatic capillaries with leucocytes. Sometimes large areas of liver tissue may be rendered unrecognisable by the capillary engorgement, and the cells may be squeezed into thin strands, or may have altogether disappeared. The cells present correspond roughly to those in the blood. Normoblasts are often seen in the capillaries. Giant cells of bone-marrow type are sometimes present. Large phagocytes ingesting red and white cells are present in a majority of the cases. Pigment is always present in moderate amount, and often gives the iron reaction.

Kidneys.—Catarrhal changes are often present. Leucocyte infiltration, in some cases destroying the tubular structure, is often found. Giant cells and pigment are frequently present. Deposits of uric acid are by no means common.

Spleen.—In a few cases the enlargement of the spleen is slight;

usually it is massive. The Malpighian bodies are small and usually atrophied. The pulp is packed with cells corresponding to those in the blood. There may be an increase of fibrous tissue. Giant cells, phagocytes, and pigmentary changes are found.

The Lymphatic Glands.—Glandular enlargement is not constant and the groups affected vary greatly. The histological change is an invasion with myelocytes, lymphocytes, and the other forms in the circulating blood. Structure is seldom obliterated so completely as in the case of lymphatic leukæmia, and many glands appear normal. Hæmolymph glands are generally more invaded than the lymph glands and may show pigmentary changes.

The Bone-Marrow.—The bone-marrow throughout the body has a pink colour and is soft in consistency though moderately tenacious. It is definitely myelocytic in character. The fat in the shafts of the long bones is in large measure replaced by hæmopoietic cells. Myelocytes are usually most in evidence, next to them red cells. In some cases there are large numbers of eosinophils, and there is always a fair number of large lymphocytes. Giant cells are scanty. Phagocytic cells are not constant. Pigmentary changes are sometimes present.

The Blood.—Macroscopically the blood seen post-mortem presents a remarkable appearance. Large greenish-yellow clots may be found in the heart and large vessels, and the vessels in some cases may contain a yellowish-white fluid resembling pus. In other cases the vessels present for the most part the ordinary appearances, but whitish clots of small size may be seen here and there.

Pathology.—The disease consists of an excessive production of leucocytes of the granular series and lymphocytes (myeloblasts) in the bone-marrow. These cells pass into the blood-stream and invade the various organs. The spleen, in virtue of its function of dealing with effete cells in the blood, has to bear the brunt of the invasion, hence the special enlargement of that organ. Since the number of leucocytes in the blood is usually much greater in myelocythæmia than in lymphatic leukæmia, the spleen is usually very much larger in the former. Nothing certain is known regarding pathogenesis. Alleged blood parasites have failed to carry conviction. Injections of leukæmic blood into animals and even into human subjects suffering from carcinoma have failed or been inconclusive. The disease occurs in dogs, cats, horses, cattle, sheep, goats, and rats, and a somewhat analogous condition is found in fowls. Injections of

blood from a leukæmic dog into healthy dogs have failed to transmit the disease.

For very much the same reasons as those given in connection with lymphatic leukæmia we regard myelocythæmia as a useless overgrowth of marrow cells, possibly due to the disturbance of the mechanism governing cell production—something akin to sarcomatosis. The origin of the conditions may differ, since a sarcoma always begins locally, while leukæmia is probably not a localised process in the same strict sense in the beginning, though possibly the great mobility of the tissue involved may account for the early diffusion of the process. As the elements involved are mainly granular cells in myelocythæmia, and as these are more highly differentiated than the lymphocytes, the disease is less malignant, and therefore in the great majority of cases runs a more chronic course than lymphatic leukæmia.

Symptoms.—(a) *Chronic Myelocythæmia.*—The disease is usually well developed before the patient has any idea of its existence. Attention is often drawn to the condition by some comparatively insignificant symptom, such as epistaxis, excessive bleeding after tooth extraction, or a pain in the side. One of our cases was a medical practitioner, whose first intimation of illness was the accidental discovery of an enlarged spleen. His blood showed 200,000 leucocytes per c.mm. and a large number of normoblasts.

Even after such a blood finding there may be complete absence of subjective symptoms for months or years, and the general nutrition of the patient remains good. Gradually increasing weakness may be complained of. Pain in the side from perisplenitis, loss of appetite, and pain and tenderness of the long bones may be complained of. The patient may begin to lose flesh. The temperature shows variations which baffle explanation. Some cases are afebrile from first to last, others may show a temperature of from 100° to 103° for a week or two at a time, and other cases may show a swinging temperature throughout the whole course of the illness. Anorexia, nausea, and thirst may be found. Attacks of diarrhœa are not uncommon, and may prove exceedingly persistent. Stomatitis is sometimes found, especially in cases with bleeding from the gums. The liver is frequently somewhat enlarged, but sometimes appears to be small because of abdominal distension. Ascites may occur as a terminal symptom.

The spleen is always enlarged to some extent and usually very greatly. It may appear to rest on the left pelvic brim. The abdomen

in such cases is greatly distorted. The spleen is usually hard and the notches along the border are easily palpated. Rarely the spleen is soft in consistency. Its size sometimes undergoes alterations. Under the influence of an intercurrent disease it may become small, and X-rays have the effect of causing a material reduction in size in most cases. In a recent case the spleen was mobile, though very large, and was sometimes found in the centre of the abdomen, sometimes at the left side, and occasionally in a nearly transverse position. In some cases the spleen is prevented from enlarging in a downward direction owing to the existence of a strong costo-colic fold of peritoneum. In such instances splenic dulness extends upwards towards the thorax.

The lymphatic glands show uncertain and very irregular enlargement. It is rarely massive. The inguinal and axillary are perhaps the most commonly involved. Pressure symptoms sometimes arise from the enlargement of mediastinal, abdominal, or pelvic glands.

There may be cardiac murmurs and the symptoms associated with anæmia as the disease progresses. Distension of superficial abdominal veins may be noted when there is much abdominal distension. In the late stages there is often œdema of the lower limbs. Bronchitis with cough is not uncommon. The sputum may contain a large number of eosinophils. Warthin describes a case which died from symptoms of œdema of the glottis. Post-mortem sufficient leukæmia infiltration of the larynx to cause stenosis was found. Pleuritic effusions may occur. Serous effusions show the usual cellular content determined by their cause, but hæmorrhagic effusions contain the same kinds of cells as are present in the blood. A case with chylous ascites has been reported. The chief cause of the milky appearance of the fluid was the presence of myelocytes. The skin is dry and pale. Lymphomatous tumours occasionally occur. Petechiæ are not uncommon. The urine shows no special peculiarities. Deposits of uric acid may occur, but are not constant, and have no relation to the number of leucocytes in the blood. There is always a heavy deposit of uric acid in the first few days after X-ray treatment is begun, presumably from the destruction of leucocytes.

Priapism is complained of in some cases. This may be due to thrombosis of the corpora cavernosa, and may call for relief by incision. The condition may persist after death. Suppression of the menses occurs in advanced cases. Menorrhagia is uncommon. Leukæmic women have given birth to healthy children, without apparent aggravation of their symptoms, but death has occurred from hæmorrhage

after abortion. Symptoms referable to the eye are not common in this form of leukæmia. Tinnitus, vertigo and deafness, sometimes from hæmorrhage into the middle or internal ear, are more frequently met with. Transverse myelitis, nerve infiltration, and hæmorrhages have been found in a small number of cases.[1] An association with osteosclerosis has been recorded in four cases.[2] The terminal stage does not differ as regards the symptoms from the terminal stage of lymphocythæmia.

(b) *Acute Myelocythæmia.*—This condition is very rare. Hirschfeld, in 1904, could find records of only six undoubted cases, and the number now on record is still very small. (We refer, of course, to cases in which the preponderating cells are myelocytes with granules. A very considerable number of myeloblast or "lymphoidocyte" cases have been reported as "acute myeloid" leukæmia. As we explained in the section on Classification we prefer, on clinical as distinguished from cytological grounds, to refer such cases to the lymphatic groups.) Acute myelocythæmia has occurred at ages between infancy and sixty-eight. There is no difference in symptoms between this and the chronic form, except their greater severity and the more rapid incidence of anæmia. The blood-picture shows variations of the same kind that occur in the more common form.

The Blood Changes. — The naked-eye appearance of the blood has none of the striking characters which are so conspicuous after death. The blood may look almost normal, but is sometimes more opaque than usual. A point often noticed is the difficulty in getting films to spread evenly, owing to the large excess of white cells.

Cases seen reasonably early show no signs of anæmia, and the shape, size, and staining reactions of the red corpuscles are not altered.

From the outset, however, nucleated red cells in the blood are a conspicuous feature of the disease in the great majority of cases. They are usually numerous enough to be found without any difficulty, but sometimes they are not to be seen. Normoblasts preponderate in the majority of cases, but megaloblasts may also be numerous. The greatest numbers we have seen when the patient first came under observation were: normoblasts, 35,000 per c.mm.; megaloblasts, 17,000. In only one case (a child) have we seen megaloblasts in the majority. The numbers

[1] Baudouin and Parturier, *Revue Neurologique*, 1910.

[2] Goodall, *Edin. Med. Journ.*, 1912, and *Trans. Med. Chirurg. Soc. Edin.*, xxxi. 1911-12.

were : megaloblasts, 15,000 per c.mm.; normoblasts, 2500. In only one case have we failed to find normoblasts throughout the whole course of the illness. We have seen as many as 7 normoblasts to every 300 white cells in a man who was doing a full day's work as a labourer, and in whom the disease was discovered accidentally.

In the later stages anæmic symptoms supervene, and the usual picture of secondary anæmia is grafted on the myelocytic blood. Hæmoglobin remains proportional to the number of red cells till anæmia supervenes, and then the colour index tends to become low. In cases with a very high white count it is difficult to estimate hæmoglobin accurately by any of the methods which depend on transmitted light, for the large number of leucocytes renders the diluted blood more or less opaque.

White Cells.—The number of white cells is, as a rule, greatly increased. In no other condition are such high counts ever obtained. The usual limits are from 200,000 to 500,000 per c.mm., but may reach 1,000,000 or more. During remissions and during intercurrent affections the leucocyte count may fall to a low figure, but even in these cases abnormal cells are apt to persist.

The chief feature of the blood is the large number of myelocytes which it contains. All varieties—neutrophil, eosinophil, and basophil—are represented. In addition to this essential feature all the varieties of normal leucocytes are increased. This is specially well illustrated in the case of the lymphocytes. If we take half a dozen cases at random the totals work out in this way—

Total counts . .	412,000	400,000	8000	116,500	136,000	451,800
Total lymphocytes . .	41,200	16,200	2240	5,825	14,820	22,590
Lymphocyte percentage	10	4	28	5	12	5

The overwhelming number of polymorphs and myelocytes generally results in the percentage numbers of the others being low, but their total numbers are always increased.

In most cases large lymphocytes are a striking feature in films. These are often specially large and their protoplasm is deeply basophil, and one is left in little doubt that these cells are really myeloblasts. But when differential counts are made, so many forms are found which appear intermediate between these and typical large lymphocytes that it is impossible to know where to draw the line of differentiation, or at least to draw it so that the separation would have any meaning to any one but the individual observer. In no other disease is the proportion

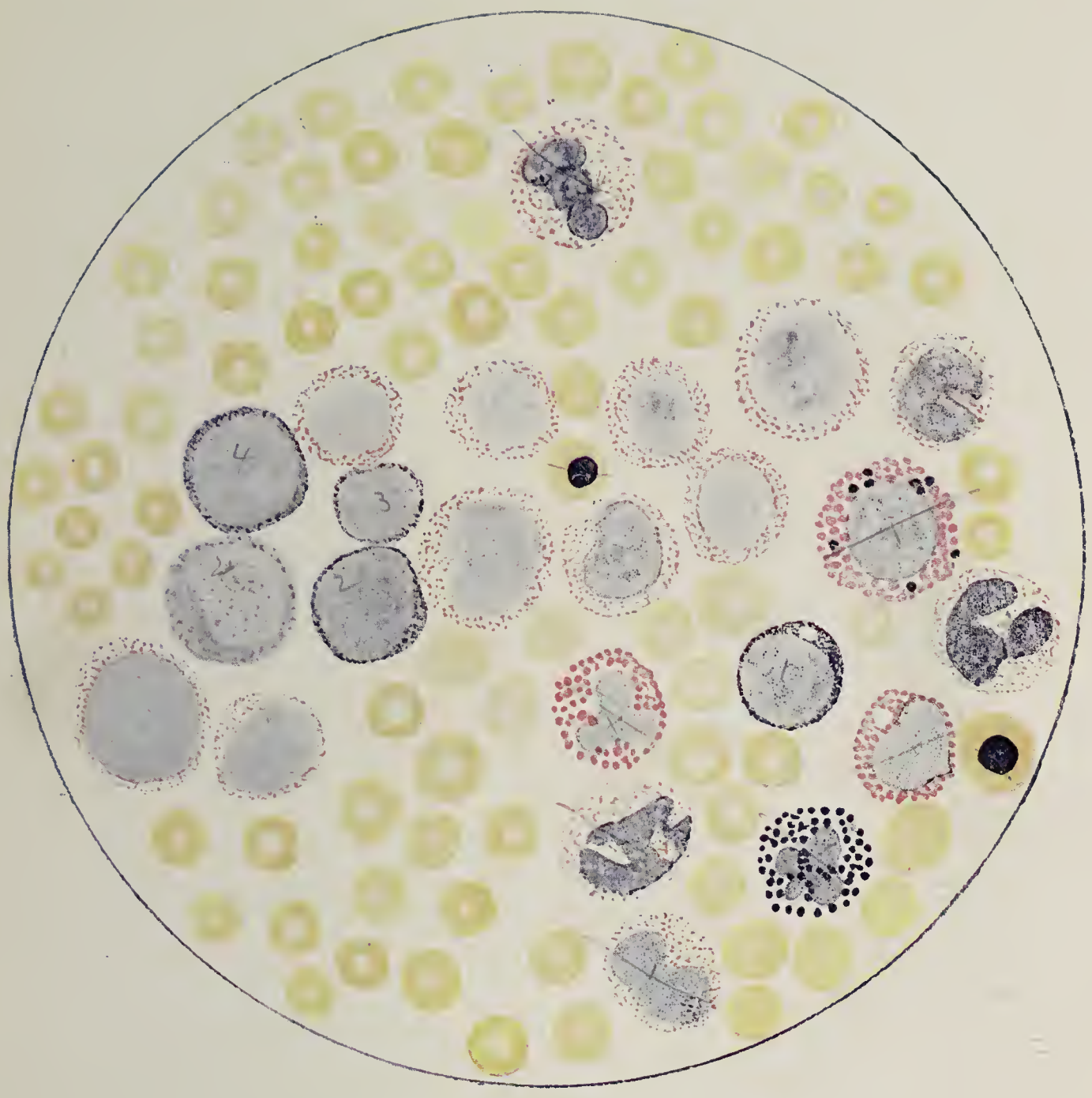


PLATE XII.—MYELOCYTHÆMIA (Jenner's Stain).

The most numerous white cells are neutrophil myelocytes. There are two eosinophil myelocytes, one with some unripe (basophil) granules. The remaining white cells are four lymphocytes, five polymorphonuclear neutrophils, one eosinophil and one basophil.
There are two normoblasts.

A. G., *pecit.*

and number of basophils so constantly high. Tomaszewski[1] has recorded a case with 303,000 leucocytes per c.mm. Of these 37 per cent. or 112,110 per c.mm. were basophils.

While the blood-picture in myelocythæmia is a very definite one, there are remarkable differences between individual cases. One may appear overwhelmingly melocytic, another may show a specially large number of eosinophils, and so on. This point may be best illustrated by the following table showing the result of enumeration and differential counts of the leucocytes made when the patient first came under observation :—

No.	Sex.	Age.		Polymorphs.	Large Lymphocytes.	Large Mononuclears.	Small Lymphocytes.	Esinophils.	Neutrophil Myelocytes.	Eosinophil Myelocytes.	Basophils.	Per 300 Leucocytes.	
												Normoblasts.	Megaloblasts.
1	M.	43	912,000	37	3	7	0·3	5·6	34	4	9	0	1
2	F.	28	350,000	48	4·6	2·4	1·2	0·9	32	3·2	6	1	0
3	F.	21	412,000	24	3	6	1	8	53·7	3	1	0	0
4	M.	45	210,000	26	7	4	0	7	53	2	1	6	3
5	M.	50	305,000	58	0·5	1·5	0·5	0·5	36	2·5	0·5	3	1
6	F.	47	170,000	10	15	1	0·5	5	65	3	0·5	0	0
7	F.	39	470,000	61	0	0	0·5	0·5	37	0·5	0·5	22	10
8	F.	32	500,000	53	3·5	1·5	1	4	24	0·5	12·5	2	2
9	F.	37	400,000	64	1·5	1	1·5	6	15	4	7	5	0
10	F.	23	8,000	42	19	3	6	4	13	1	12	6	12
11	M.	33	116,562	50	4	0	1	1·5	41	2	0·5	7	7
12	F.	35	380,000	66	4	8	1·5	0·5	18	1	1	3	0
13	M.	40	451,875	18	2	2	1	2	68	1	7	0	0
14	M.	42	238,000	41	23	4	4	6	11	2	9	6	6
15	M.	31	320,000	63	4	3	1	1	20	5	3	2	4
16	M.	51.	136,000	77	3	6	3	2	2	1	6	2	0
17	M.	50	640,000	35	3	3	1	1	47	8	2	6	3
18	M.	37	580,000	33	12	4	4	2	26	5	14	18	12
19	M.	29	450,000	60	3	2	4	3	24	2	2	9	9
20	M.	13	212,000	49	15	5	2	3	15	5	6	0	0
21	F.	9	130.000	32	15	7	3	5	22	3	13	6	33
22	M.	60	415,000	59	2	1	0	5	27	1	5	6	18
23	F.	7	59,000	53	13	3	3	3	22	2	1	9	14
24	F.	42	420,000	48	10	3	1	3	16	4	15	0	0

The table shows the following variations :—

Polymorphs	10	to 77	per cent.
Neutrophil myelocytes	2	„ 65	„
Lymphocytes (all sorts)	3	„ 13	„
Eosinophil polymorphs	0·5	„ 8	„
„ myelocytes	0·5	„ 8	„
Basophils	0·5	„ 15	„

[1] *Folia Hæmatologica*, xii. *Archiv*, 1911, 115.

This marked variability was pointed out by Ehrlich long ago, and, like him, we do not find that the alteration of percentages corresponds to any noticeable clinical differences or pathological variations. Another striking feature of myelocythæmia is the capricious way in which the proportions of cells may vary from time to time. The difference in the individual case may be illustrated by taking the first one, in which, on four separate occasions, the percentages were as follows:—

Polymorphs	18	19	31	7
Myelocytes	68	44	46	58
Lymphocytes	2	28	18	34
Basophils	7	7	1·6	6
Eosinophils	5	2	3·4	5

The blood-plates may be present in normal nnmbers or may be considerably increased.

Summary.—In a typical case the blood changes may be said to consist of—

1. A great increase in all varieties of the white cells.
2. A great invasion of myelocytes.
3. The presence of numerous nucleated red cells without necessarily any anæmia.

Effect of Intercurrent Disease on the Blood.—The blood-picture of myelocythæmia may be entirely altered and even masked altogether by the presence of an intercurrent affection. Febrile diseases are specially likely to have this effect. We have seen the leucocyte count fall from 225,000 to 8000 during the course of a severe attack of influenza. It is exceptional for the qualitative changes to be entirely abolished, so that the combination of the splenic enlargement and suspicious blood-picture might lead to a diagnosis of the condition, even in the presence of a complication. In other cases the complication has no effect on the blood-picture, but more frequently the proportion of polymorphs is increased, that is to say, there is an ordinary leucocytosis superadded, though the total count may not be much altered. Differences of several thousand cells occur without any special reason in myelocythæmias from day to day, if the blood be counted regularly, so that it is not easy to be sure whether a special increase is necessarily due to a complication.

Diagnosis.—The diagnosis depends on the blood examination, and cannot be made without it. The only possible difficulty is the occurrence of a remission, or the incidence of an intercurrent affection, as discussed above. Ehrlich has laid stress on the importance of a proportional increase of basophils in diagnosis, and in one case we saw a

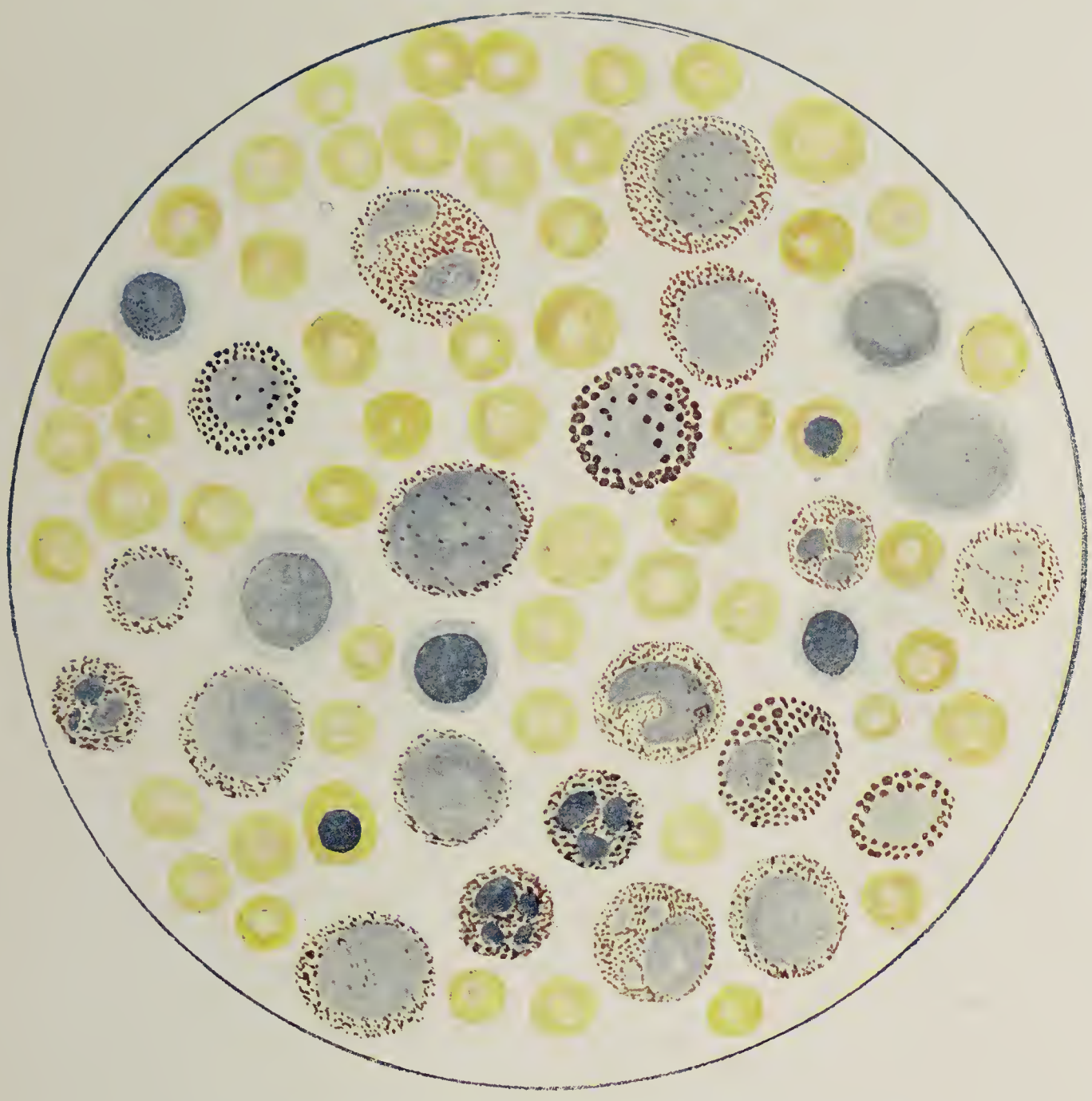


PLATE XIII. – MYELOCYTHÆMIA (Ehrlich's Triple Stain).

A. G., *fecit.*

leucocytosis ranging about 12,000, with a basophil percentage varying from 12 to 28 per cent., and an occasional neutrophil myelocyte, precede, by some months, the onset of a typical myelocythæmia. We have seen other cases, however, come into hospital suffering from anæmia with a high percentage of basophils and eosinophils, and in one case a slight enlargement of the spleen, whose blood, with ordinary treatment, became absolutely normal, and remained so for some months, until the patients dropped out of observation.

Prognosis.—Prognosis is absolutely unfavourable. The acute cases have died in from fourteen days to eleven months. The duration of the chronic cases is not easily stated, on account of the insidious onset. Most cases are likely to live for at least six months after they first come under observation. They probably all die within four or five years. While there is not the same tendency to complete remission and apparent return to health as in pernicious anæmia, the progress is not uniformly downwards. As the result of treatment, and sometimes without it, remissions may take place. In these the spleen may diminish in size, sometimes considerably, and the leucocyte count may drop greatly, even perhaps to normal, although abnormal cells can generally be found. In other cases the spleen and white count may remain unchanged, but the weakness and anæmia from which the patient suffered may pass off. Sooner or later, however, the patient relapses. There is not the same tendency to intercurrent disease of an infectious or inflammatory type as is found in lymphatic leukæmia. This is perhaps accounted for by the better protection afforded by the large number of granular leucocytes in the blood.

The fatal termination is generally the direct result of anæmia and wasting, but a cerebral hæmorrhage or hæmorrhage from mucous membranes, or attacks of delirium or coma, may immediately precede the end.

Treatment. — Treatment is unsatisfactory. As long as patients are able to go about and take open-air exercise they should be encouraged to do so. Should subjective symptoms of weakness or anæmia supervene, patients should be kept in bed, and, of course, symptomatic treatment of various kinds may have to be resorted to. Arsenic is always worth a trial, given in increasing doses, as in pernicious anæmia. In the days before X-rays a fair proportion of cases responded to this treatment, and remissions followed. Care should be taken to avoid causing diarrhœa, which is not well borne. In some cases arsenic produces no effect, and need not then be continued. If the colour index

be low, iron may be added with advantage. We have treated one case with atoxyl and another with soamin without bad or good effect in either case. Both cases had been refractory to ordinary arsenic. Since the introduction of salvarsan we have only felt ourselves justified in treating one case with this remedy. The full dose was given intravenously. This was followed by the usual rigor and sickness, with a little diarrhœa, and a swinging temperature lasting for five days. There was no effect whatever on the spleen or the blood, and though the patient, after recovering from the temporary disturbance, said that she felt stronger, as blood cases often say they do after salvarsan treatment, we did not feel justified in repeating the injection. This patient was refractory also to ordinary arsenic and to X-rays, and has since died.

Great things were expected of X-rays when they were first used in the treatment of myelocythæmia. It is beyond doubt that remission can be brought about in a larger proportion of cases than with arsenic, and that the reduction in size of the spleen and in the number of the leucocytes is often more rapid. In some cases the spleen seems to melt away almost from day to day, while the leucocytes may drop by a hundred thousand, or even more, in a week. But in other cases there is a complete want of response to the treatment, and all grades of response between these extremes are met with. We have not been able to determine the factors on which this difference depends. Speaking generally, early cases in good general health do better, but this rule does not always hold, as we have seen old cases do well and presumably early cases prove refractory. But X-rays do not cure the disease, even in successful cases. Recurrences follow, and second courses of irradiation are not usually so successful as the first. The interval of remission may be long. We treated a case very successfully three years ago, and heard of her recently as being symptomatically well.

When X-ray treatment was first started it was applied over the spleen only, but it has been found that better results are obtained by irradiating the long bones also. The body is mapped out into areas, and these are treated in turn. The applications should be made from ten to twenty minutes at a time every second or third day. Great care must be taken to avoid burns. In a few cases obscure toxic symptoms have followed irradiation, of the same kind as those seen when X-rays are used in acute lymphocythæmia. In cases which react to treatment there is first destruction of the circulating leucocytes, especially those of the granular series, but as it is continued the formation of fresh leucocytes is inhibited. The lymphocytes are much less affected than

the neutrophils, basophils, and eosinophils, and their resistance may be so marked that the blood-picture may at one stage resemble closely that of a lymphocythæmia. During treatment the blood must be fully examined at least once a week, for it is possible to carry the process so far as to exhaust the marrow completely. This has also been proved experimentally in animals. In one of our cases this was well brought out. The patient was responding well, was improving in weight, the spleen was diminishing, and the whites falling rapidly to normal. Our resident physician had been counting the whites regularly, but had omitted to estimate the reds and hæmoglobin for some time. On our return from a holiday we were struck by the patient's pallor, and on examining the blood found that it presented the complete picture of pernicious anæmia—reds, 3,340,000; hæmoglobin, 80 per cent.; colour index, 1·2; whites, 3430, with a fair number of megaloblasts, while the normoblasts and myelocytes had disappeared. Stopping the X-rays and giving arsenic soon restored the reds to a more normal condition. The accompanying table of this case illustrates the course of events. We append also the counts of a case refractory to X-rays which died of pneumonia about six weeks after leaving hospital. It is unnecessary to quote more of the successful cases; they generally pursue the same course as that given.

	Reds.	Hæmo-globin.	Colour Index.	Whites.	
10/1/09	4,800,000	90	0·9	600,000	Before X-ray treatment.
15/1/09	...	...	...	534,000	After one exposure.
21/1/09	...	...	...	483,000	On X-rays thrice weekly.
10/2/09	...	...	...	373,000	
24/2/09	...	...	...	277,000	,, twice weekly.
17/3/09	...	...	...	306,000	
2/4/09	...	...	...	381,000	Arsenic added to X-rays.
9/4/09	...	...	...	141,000	
13/4/09	...	...	...	93,000	
20/4/09	...	...	...	10,900	
27/4/09	3,340,000	80	1·2	3,400	X-rays stopped, arsenic stopped.
4/5/09	3,700,000	78	1·1	3,800	
11/5/09	3,500,000	73	1·05	3,400	Arsenic begun on 12/5/09.
18/5/09	4,150,000	72	0·87	5,900	
25/5/09	4,340,000	73	0·84	13,000	
22/6/09	5,010,000	80	0·80	9,200	Discharged from hospital, spleen just below costal margin.
		(many intermediate counts are omitted)			
4/9/09	5,900,000	85	0·71	78,000	Symptomatically well; went home and kept well for about a year, but died rather suddenly of pneumonia.
			A. P. (refractory case)		
16/2/11	2,450,000	40	0·8	319,400	X-rays begun 18/2/11, and continued twice weekly.
25/2/11	...	...	...	292,000	
4/3/11	...	...	...	260,000	
11/3/11	...	...	...	350,000	
20/3/11	...	...	...	350,000	Salvarsan intravenously.
24/3/11	...	...	...	337,500	
2/4/11	...	...	..	345,500	
18/4/11	3,000,000	52	0·86	400,000	Spleen had not diminished in size at all; general health rather improved.

Thorium X has been tried, but is not so useful as the X-rays.

Benzol has recently come into favour in the treatment of myelocythæmia. The observation was made by Sellings that workers in benzol vapour suffered from anæmia and leucopenia. Experiments on rabbits showed that the drug had an inhibitory effect on the activity of the bone-marrow. On these grounds benzol has been extensively used.

Very variable results have been noticed. Distinct benefit has been reported in several cases. In many of these, however, the amelioration has been transient. In some cases the drug sets up gastro-intestinal disturbance, and cannot be tolerated. In other cases it has set up albuminuria. Again, it has failed to bring about any general improvement, although the leucocyte count has lessened and the size of the spleen diminished, and yet again attacks of epistaxis and other hæmorrhages have followed its administration.

It is particularly important to note that benzol may bring about a leucopenia just as this may follow an excessive course of X-ray treatment. It is therefore imperative that its action should be carefully checked by frequent enumerations of the white cells, and the administration should be stopped while the leucocyte count is still well above the normal, since a fall may continue for some time after the drug has been stopped. Benzol is best administered in the form of capsules containing 5 ♏ along with 5 ♏ of olive oil. One of these may be given thrice daily, and if no untoward symptoms result the dose may be very gradually increased to 20 ♏ thrice daily, which is about the usual limit of tolerance.

In our own experience we have met with no very striking success and with no untoward result, except that in some cases the drug has not been tolerated by the stomach.

Two of our cases developed a fairly severe febrile reaction with gastro-intestinal disturbance when the drug was pushed, and at the height of this the leucocyte count, which had been 240,000 and 184,000, fell to 7000 and 24,000 respectively. After the fever was over the count returned in both cases to the previous height, or rather above it. Such a diminution in the course of an intercurrent febrile attack is common in myelocythæmia, and of no significance from the prognostic point of view.

There is no doubt, however, that a considerable reduction in the leucocyte count is generally effected, and our impression is that in all cases benzol is worth a trial. As a rule it is not so efficacious as the X-rays, but it can be combined with X-ray treatment, and may be

regarded as a fairly good substitute when the X-ray treatment is not available.

The only other drug which deserves mention is naphthalene tetrachloride. It has occasionally brought about improvement. The initial dose is 4 gr. thrice daily, in cachets, which may be increased.

In view of the effects of infections on the blood, attempts have been made to treat cases by the use of vaccines. These have all failed. Excision of the spleen has done no good in the few cases that have survived the operation, and as the seat of the disease is in the bone-marrow, one cannot reasonably expect that splenectomy would be of service. All operative procedures are extremely dangerous and should be avoided.

3. Mixed Forms of Leukæmia

Cases of leucocythæmia are sometimes met with in which the blood-picture is intermediate between that of myelocythæmia and lymphocythæmia.

The following case[1] may serve as an example:—

Child, aged five. Great enlargement of glands and spleen, retinitis. Red corpuscles, 2,610,000; nucleated red cells, 4000 per c.mm.; leucocytes, 240,000 per c.mm.; polymorphs, 16 per cent.; lymphocytes, 54 per cent.; eosinophils, 9 per cent.; mast-cells, 4 per cent.; myelocytes, 17 per cent.

A few observations on the course of such cases have shown that they may arise in two ways:—

1. Cases of myelocythæmia may become "mixed" cases by the failure of the marrow to elaborate the granular type of cell, or because the morbid process so accelerates the output of cells from the marrow that there is no time for the elaboration of the granules. An extreme instance of such a case is recorded by Wilkinson.[2] Patient was suffering from symptoms of myelocythæmia. The blood was typical but for the presence of nearly 50 per cent. of lymphocytes. In two days' time the blood examination revealed a typical lymphatic leukæmia.

2. Cases of lymphocythæmia may become "mixed" cases by the lymphocyte proliferation acting as a stimulus to the parts of the marrow as yet unaltered, with the result that a large number of myelocytes make their appearance, usually accompanied by an increase in the number of nucleated red rells in the blood.

[1] Fowler, *Internat. Clinics*, 1903.
[2] Wilkinson, *Lancet*, 20th June 1903.

Another aspect is suggested by Herxheimer,[1] who has published a case of "combined lymphatic and myeloblast leukæmia," in a male aged 16. There were 70,000 leucocytes per c.mm. Of these 69·8 per cent. were lymphocytes, and 25·4 per cent. were myeloblasts.

In the spleen and most of the lymph glands the lymphoid follicles were enlarged. The bone-marrow and liver also showed a marked lymphocyte increase with smaller collections of myeloblasts. In a mediastinal tumour in bronchial glands, and in the kidneys, the cellular invasion consisted almost entirely of myeloblasts. The case is regarded as an acute development of myeloblast leukæmia in a case of longer standing lymphatic leukæmia. The oxydase reaction is relied on in making the distinction, and the case is thought to afford evidence of the dual origin of lymphoid and myeloid tissues.

It appears to us that the case might be used as an argument in the contrary direction. It as readily suggests that the distinction between lymphocytes and myeloblasts is a somewhat arbitrary one, and that the oxydase reaction in round nucleated cells is a matter of no particular significance.

4. Chloroma

A disease characterised by a leukæmic condition of the blood and by the formation of tumours, sometimes of a greenish colour, throughout the body, but specially associated with bone. The condition is very rare. Dunlop, in 1902, could find records of only twenty-seven cases. The number reported up to the present time is about sixty.[2]

Etiology.—The disease is chiefly one affecting children, but it also affects adolescents, and has occurred in a few instances after thirty. A larger number of cases have occurred in males and females.

Morbid Anatomy and Pathology.—The gums are often swollen, soft, and show a pale greenish tinge. Nodules may be seen in the intestine. The lymphoid masses may show a greenish colour. The heart sometimes shows green-coloured patches on its wall. The liver is enlarged to a slight extent in some cases. The kidneys are generally enlarged and may be dotted over with greenish nodules under the capsule. The spleen is somewhat enlarged but is seldom anything like the size which may be reached in leukæmia. The lymphatic glands are enlarged and pale; some of them have a green colour. The thymus

[1] *Zentralb. f. Allgem. Path. u. Path. Anat.*, xxiv. 897.

[2] Hall, *Proc. Roy. Soc. Med.*, ii. 1909, gives bibliography.

is usually unaffected. The bone-marrow may be dark red in colour, but in many of the bones the fatty marrow appears to be replaced by a greenish pus-like material.

Tumours.—The striking feature of the disease is the presence of green-coloured tumours, chiefly in connection with the periosteum of the bones throughout the body, but specially numerous in connection with the bones of the skull and face. The tumours may be a bright pea-green on section, but the colour soon fades. They may cause erosion of bone.

On microscopic examination the infiltrations of organs and the growths are found to consist of round cells, having in the majority of cases the general characters of lymphocytes. In some cases, however, some of the cells show granulations corresponding to the neutrophil or eosinophil leucocytes. In one case we found very large numbers of basophils. The microscopic appearances of the organs are in other respects similar to those found in cases of leukæmia.

The Pigment.—Little is known regarding the nature of the green pigment. It fades fairly rapidly on exposure to air, and has altogether disappeared from microscopic sections by the time they have been prepared. The pigment is affected by differences in its amount of oxygen. Dunlop found that the colour could be restored by the application of reducing agents. Hall, Hebb, and Bernstein [1] found that it was bleached by peroxide of hydrogen. On the other hand, Trevithick [2] found that the green colour was restored by the application of peroxide of hydrogen, an observation which we could confirm in one case and not in another. The pigment is insoluble in alcohol, chloroform, and ether. It is at least partially soluble in 3 per cent. acetic acid, boiling water, and possibly boiling alcohol and ammonia. Pope and Reynolds regard it as a fatty acid combined with iron.

The pathogenesis of the disease is unknown. This disease affords strong evidence in favour of the view that the leukæmias are of the nature of sarcomata. In chloroma there is a useless hyperplasia of the cells of bone-marrow. These cells pass into the blood-stream and invade all the tissues and organs of the body. They may give rise to metastatic growths, and for some unknown reason the metastases seem to have a selective, though by no means exclusive, affinity for periosteum.

Symptoms.—As in ordinary leukæmia, symptoms are not much in

[1] *Proc. Roy. Soc. of Med.*, 1909.
[2] *Lancet*, 22nd August 1903.

evidence until the disease has made considerable progress. Patches of ecchymosis, soreness of the gums, deafness, hoarseness, or the presence of actual tumours or proptosis may call attention to the condition. Much more rarely the patient complains of general weakness or ill-health.

As the disease develops the tumours about the face and head enlarge, and become very striking. There may be proptosis to such an extent that the patient cannot close the eyes. The conjunctivæ may become infiltrated with either a flesh-coloured or greenish-yellow growth, leading to blindness. The intracranial growths may cause vascular engorgement, thrombosis of sinuses, or compression of cranial nerves or even of the brain. The nervous tissue is not actually invaded. Deafness and other aural symptoms are common from growths in the middle or internal ear. Nodular eruptions may appear on the skin all over the body. The usual lesion is in the form of flat-topped nodules, varying in size from a pin's head to a shilling. They are generally painless and freely movable. There may be extravasations of blood in the eye, and retinitis and optic neuritis may occur. There is a marked tendency to hæmorrhages, especially from the gums and mucous membranes. Petechial and other hæmorrhages into the skin occur. In one case a profuse hæmorrhage took place from the orbit.

The Blood Changes.—The usual picture is that of a typical lymphatic leukæmia. This is, however, by no means constant.

In Bramwell's[1] case the total number of white cells was 8000 per c.mm., with 95 per cent. of lymphocytes. In Pribram's[2] case there were 10,000 white cells at first, and later their number fell to 800. Again, cases occur in which there is a large proportion of myelocytes. As many as 32 per cent. have been noted by more than one observer. Eosinophils and basophils may be numerous. There is practically always some degree of anæmia, and as the case advances it becomes very severe.

Diagnosis.—The diagnosis depends upon the presence of the tumours, or of some feature such as proptosis indicating their existence, along with the characteristic blood changes.

Prognosis.—Cases of chloroma are quite hopeless. The fatal termination may be brought about in the same ways as in leukæmia, but with a tendency to more rapid emaciation and with a greater likelihood of some pressure symptom occurring.

[1] *Trans. Edin. Med. Chirurg. Soc.*, xxi. 1902.
[2] *Münch. med. Wochenschr.*, 1909, No. 40, 2086.

Treatment.—Treatment is on the same general lines as that of acute lymphatic leukæmia.

Leucanæmia

This term was introduced by Leube to denote a condition of the blood presenting the chief features of myelocythæmia and of pernicious anæmia.

The red cells may fall to below one million. The colour index becomes high, and there are numerous megaloblasts and normoblasts. The white cells show a large number of myelocytes and lymphocytes, but eosinophils and basophils are scanty. The qualitative changes may be seen without any actual increase in the number of leucocytes. In one or two cases there has been an actual leucopenia, and if a case were seen at that time there might be ground for a diagnosis of pernicious anæmia.

In the cases which have been examined after death the general appearances have been those of myelocythæmia. The liver in a few cases has shown marked siderosis, which is precisely what we find in a few cases of myelocythæmia. The marrow shows a myelocytic reaction, but lymphocytes are abundant. There is a considerable amount of megaloblastic change. These appearances might lead one to suppose that leucanæmia was a mixture of the two conditions. This is so far true. But it may be pointed out that in nearly all cases of pernicious anæmia there is a myelocytic reaction on the part of the red marrow, and that in all cases of myelocythæmia the marrow shows a varying degree of megaloblastic change.

Leucanæmia is simply a phase in the course of cases of leukæmia, and illustrates what we have already said regarding the great variability of the blood-picture in that disease within certain definite boundaries. It further emphasises the necessity of repeated examinations of the blood in any atypical or ill-defined case before a conclusion is reached. We have seen the blood-picture of "leucanæmia" develop in the course of cases of myelocythæmia as the result of treatment by X-rays or without apparent cause, and at a later stage the typical blood-picture of myelocythæmia has returned.

We think the term could with advantage be dropped. It may indicate a certain symptom-complex which might be understood by the expert, but he is likely to maintain a healthy scepticism until he has seen the figures. To the practitioner who has not specially studied the literature of hæmatology the term is likely to be meaningless.

CHAPTER XXII

LYMPHADENOMA—HODGKIN'S DISEASE

Definition.—A disease characterised by progressive enlargement of lymphatic glands, hyperplasia of lymphoid organs, and anæmia.

Etiology.—The disease is most common between the ages of thirty and forty. It is fairly common below twenty, less common between forty and fifty, and there is again an increase after fifty. The disease is three times as common in males as in females. Some cases have suggested an infective origin. Rolleston refers to a case beginning in the axilla after a poisoned finger. It has followed disease of the ear, chronic nasal or pharyngeal catarrh, local injuries, and such operations as the removals of tonsils.

Pathology.—There is extensive enlargement of glands either throughout the body or in large groups. The glands are mostly discrete, but a few of them may be confluent. The spleen is enlarged to a variable extent in over 75 per cent. of cases, and in one or two cases the suggestion has been made that the splenic enlargement was the primary lesion. The liver may be slightly enlarged. There are sometimes collections of cells which give rise to "suet-like" nodules, visible to the naked eye, most often in the spleen, but sometimes in liver and kidney also.

The histological change in the lymphatic glands is a diminished activity of the germ centres, so that the reticulum is not obscured and the sections have a homogeneous appearance. There is a great prominence and proliferation of the endothelial cells and cells of the reticulum. Some of these cells attain a large size and contain four or more nuclei. These are "lymphadenoma cells," and differ from the giant cells of tuberculosis in their smaller size, and in the structure of the nuclei. Eosinophil cells are nearly always present, sometimes in small numbers, sometimes very abundant. They are often of "myelocyte" type, and are probably produced locally and not immigrants from the bone-marrow. In the early stages there may be little or no formation of the

giant cells, and in the later stages there is always a great increase of fibrous tissue. There is no essential difference between the "hard" and "soft" type of enlarged gland. The "soft" type is the early stage, the "hard" the later one. In the same group of glands the two stages may be found.

The spleen is fibrous. The Malpighian corpuscles are present but are small. Cells of the reticulum and endothelial cells proliferate, and giant cells of the lymphadenomatous type are generally abundant. Eosinophils are in varying amount. The nodules in the liver and other organs consist of lymphocytes. They are surrounded by a reticulum, and according to Adami they develop from the lymphocytes normally present in the fibrous tissue of the perivascular sheaths.

In most cases there is a moderate increase of myelocytic activity in the bone-marrow, and in many cases a great increase of eosinophils has been noticed.

The widespread distribution of the lesions is to be explained by their origin in lymphoid tissue and not by a process of metastasis. The exciting cause, whatever that may be, seems to affect lymphoid tissue over a large area. The general picture is much more suggestive of a general irritation than of malignant disease.

The actual cause of the disease is unknown. Much bacterial research has been made with the object of throwing light on the subject. White and Pröscher described a spirochæte as occurring in the glands. This has not been confirmed. Fränkel and Much have found a bacillus morphologically identical with the tubercle bacillus but not acid fast. Diphtheroid organisms apparently similar have been described by Negri and Mieremet.[1] Bunting and Yates[2] have also found bacteria which they think identical with those described by Negri and Mieremet. They have named the organism *Corynebacterium granulomatis maligni*. Billings and Rosenow[3] have isolated an organism in twelve cases—nine in pure culture—and have had some success with vaccines prepared from cultures. Attempts to inoculate the disease into animals have all failed or at least been inconclusive.

Symptoms.—The first indication of the disease is glandular enlargement. The cervical glands are more frequently affected than others; after these in order of frequency are the axillary, inguinal, retroperitoneal,

[1] *Centralb. f. Bact.* 1913.
[2] *Arch. of Int. Med.*, xii. 1913.
[3] *Journ. Amer. Med. Assoc.*, November 1913.

mediastinal, bronchial, and mesenteric. A division can often be made into cases in which the glandular enlargement is mainly superficial, cases in which the symptoms are mainly due to intrathoracic enlargements, and cases in which the symptoms are mainly abdominal.

Superficial Gland Form.—The primary glandular enlargement may be in existence for weeks, months, or even a couple of years before other symptoms become marked. The size of the glands may show great fluctuations. During febrile attacks new groups of enlarged glands may become noticeable, and glands previously involved may become larger and softer. In afebrile intervals the glands often become smaller and firmer. The glands are generally firm and elastic, and are usually discrete and freely movable. In a few cases they may become confluent, and in some instances they are quite soft to the touch. Soft and hard glands may exist in the same neck, and soft glands may become hard and hard glands may become soft.

The Thoracic Form.—The enlargement of glands in the thorax may give rise to symptoms similar to those of mediastinal tumour. As a rule the occurrence of the intrathoracic growths is a late development, but in rare instances it constitutes the earliest and main feature of the disease. There may be pressure on the œsophagus leading to dysphagia. Pressure on veins may lead to great engorgement of superficial veins of the neck, face, and arms, with cyanosis, and sometimes even exophthalmos and œdema of the conjunctivæ. There may be pressure on the trachea or bronchi giving rise to great dyspnœa. Sometimes the lymphadenomatous growths set up bronchitis or pleurisy, and in the latter the effusion has been chylous in a few instances. The dyspnœa and fever may suggest pneumonia. Pressure on the recurrent laryngeal nerve may cause paralysis of a vocal cord.

The Abdominal Form.—The abdominal manifestations of lymphadenoma usually follow some time after the superficial glands have been enlarged. There are instances, however, in which the retroperitoneal glands have been primarily attacked. In one of our cases the first gland to be attacked was apparently the most superficial of the glands lying along the left external iliac artery. The presence of these glands may suggest a diagnosis of tuberculous peritonitis. Stuart M'Donald refers to a case in which pain and resistance in the upper part of the abdomen led to an operation for a supposed leaking gastric ulcer. Pressure by the enlarged glands may lead to intestinal obstruction or dilatation of the colon, and symptoms may simulate appendicitis. Profuse diarrhœa is a rare symptom. Pressure on the bile ducts may set

up jaundice, which may vary with variations in the size of the glands and often corresponds to febrile attacks. Jaundice is a fairly common symptom towards the end. A degree of biliary cirrhosis may be set up. Either from pressure on the portal fissure or from the growths elsewhere setting up irritation ascites may occur. It is generally serous, but is sometimes chylous, and in a few instances a pseudo-chylous ascites has been found. Pressure on the inferior vena cava may cause albuminuria and œdema of the lower limbs, and pressure on the ureters may interfere with the excretion of urine. Sciatica and other pains may be set up by pressure on the nerves of the lumbar and sacral plexuses.

The Liver.—The liver is by no means always enlarged, but in some cases its size may be considerably increased. The enlargement may come on suddenly in the course of a febrile attack. Enlargement of the liver without enlargement of superficial glands may give rise to very considerable difficulties in diagnosis. Abscess of the liver may be simulated in febrile cases, and congenital syphilis may be suggested in a young subject.

The Spleen.—The spleen is somewhat enlarged in most cases. It is nearly always enlarged in abdominal cases, and in a few instances splenic enlargement may be the outstanding feature of the disease. Symmers has published a case in which there was primary lymphadenoma of the spleen. In this case and in others in which the spleen and retroperitoneal glands are alone involved the resemblance to splenic anæmia may be very close. Parkes Weber records a remarkable case in which there was at one time enlargement of superficial glands. At a later period the glandular enlargement had disappeared, and there was enlargement of the spleen, ascites, and anæmia with leucopenia. Post-mortem examination revealed enlargement of thoracic and abdominal lymph glands. Enlarged glands in the hilus of the liver probably accounted for the ascites. The diagnosis was confirmed with the microscope. In malarial districts the splenic cases may suggest that disease.

Temperature.—In the early stages, except in very acute cases, there is usually no rise of temperature, but sooner or later fever supervenes. Three distinct types were distinguished by Gowers—(1) A persistent mild fever with a diurnal variation of not more than a degree and a half. (2) A high irregular temperature with morning remissions to 100° F. This type is especially liable to occur in the later stages, and as it may then be accompanied by rigors and perspirations, a septic condition may be closely simulated. (3) An intermittent fever lasting for about ten days or a fortnight, succeeded by an apyretic interval of about the

same duration. The temperature, as a rule, rises about a degree each evening and falls about half a degree each morning, so that at the end of a week it has reached 103° F. The following week the morning fall exceeds the evening rise, so that the temperature is again normal at the end of the second week. This relapsing fever may continue for over a year, and persist till death takes place, or merge into the second form. During the pyrexial periods the symptoms are aggravated. The glands may enlarge and the skin over them may redden. The spleen becomes bigger. The patient emaciates and suffers from dyspepsia and the usual symptoms of fever. In some of these cases without much enlargement of superficial glands a diagnosis of typhoid fever might be thought of. In some cases there are long remissions without fever, sometimes preceded and always followed by fever of one of the above types. In our experience the third type is commonest (in true lymphadenoma) during the course of the disease, merging towards the end of the case into the second type.

Cutaneous Symptoms.—Intense itching of the skin is an uncommon and capricious but sometimes a very distressing symptom. Loss of hair and changes in its texture have been noticed. Bronzing of the skin sometimes occurs. Bramwell records two cases in which bronzing of the skin and leucodermia preceded any noticeable enlargement of glands. It is possible that such cases are to be accounted for by interference with the functions of the suprarenals. Lymphadenomatous nodules sometimes occur in the skin, and are subject to the regressive changes which are seen in the glands. Erythema, dermatitis, and bullous eruptions have occurred. Purpura has been described. Most of the cases were probably leukæmia, but in the anæmic stage purpura sometimes does occur in true lymphadenoma.

Nervous Symptoms. — In some cases symptoms suggestive of such lesions as tabes have occurred. Tremor, delirium, stupor or coma may be seen as terminal symptoms.

The Blood Changes.—In the early stage the blood may show no change. As the disease develops there is always anæmia, which may become severe. The red cells may fall to 2,000,000 or even fewer, and normoblasts may be present. The colour index is lowered. The number of white cells may show no change. The idea that there is an increase of lymphocytes in lymphadenoma dies hard. In a quite recent paper it is seriously suggested that the number of leucocytes is from 10,000 to 12,000, with 51 per cent. of lymphocytes. This is not our experience.

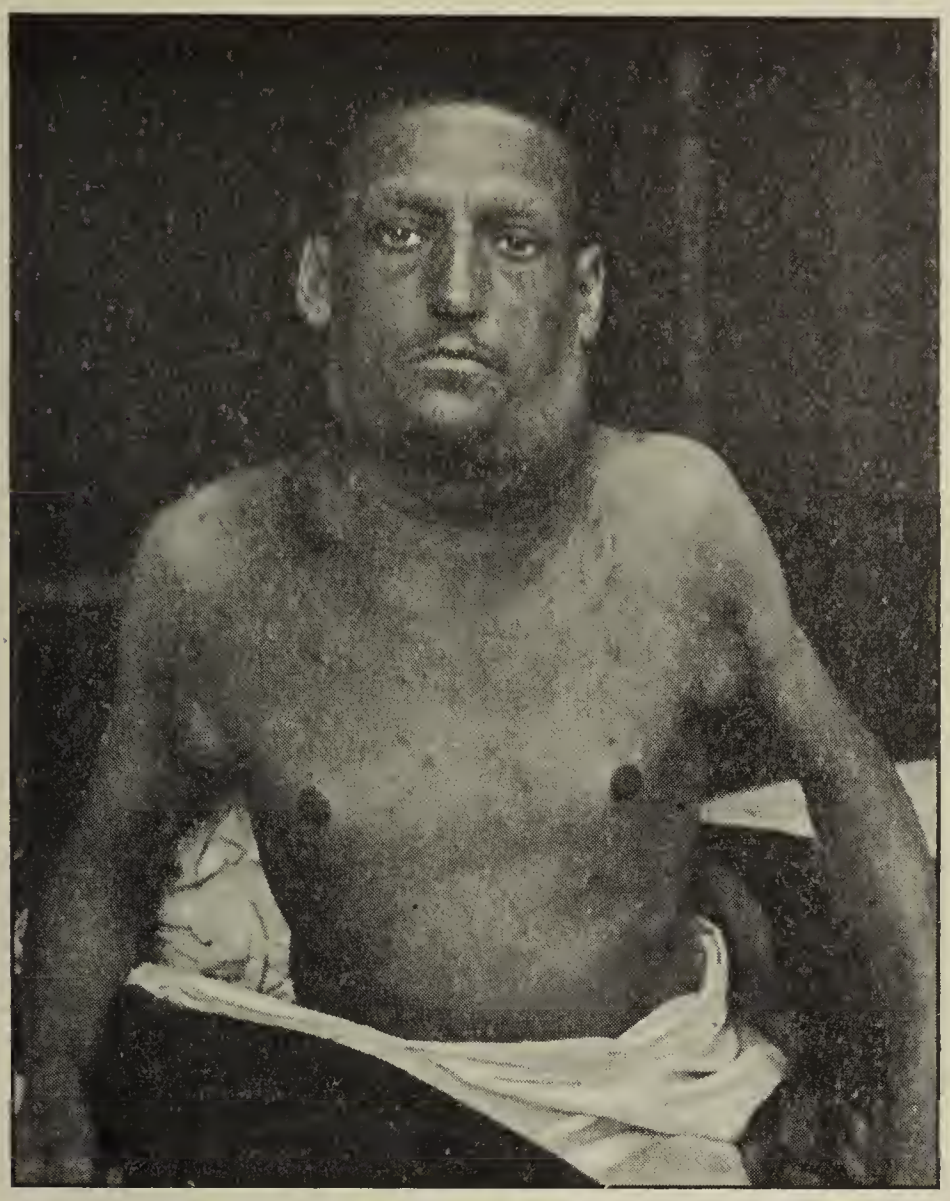


FIG. 25.—CASE OF HODGKIN'S DISEASE.



FIG. 26.—SAME CASE, THREE MONTHS LATER.

In some cases there is little alteration in the leucocyte picture from first to last. In some cases the polymorphs are diminished as an expression of the ill-health of the patient. Such cases of course show a "relative lymphocytosis." Much more commonly there is a slight leucocyte increase due to an increase in the number of polymorphs. This is more marked in the febrile attacks, the polymorph percentage and the leucocyte count often increasing in proportion to the temperature.

Considerable fluctuations in the leucocyte count may occur. In the case illustrated in Figs. 25 and 26 the count (in thousands per c.mm.) on 9th May was 40, but by the 11th it had fallen to 17. This was followed by a steady rise to 61 on 1st June, and a somewhat steady sequence of rise and fall, each phase extending over ten days, then ensued. The larger counts occasionally, but by no means constantly, corresponded to febrile attacks. Several times a diurnal variation of 10,000 leucocytes was found. The evening count was usually lower than the morning one.

Occasionally there is a marked eosinophilia. In one of our cases there was a slight increase of basophils as well as of eosinophils. The white cells numbered 12,000; polymorphs, 78 per cent.; lymphocytes, 15 per cent.; eosinophils, 4 per cent.; and basophils, 3 per cent. In another case there was a high polymorph leucocytosis to begin with, and later this was associated with a high degree of eosinophilia, which persisted till the patient died.

The glycogen reaction is sometimes mildly positive at the height of febrile attacks in lymphadenoma, and is fairly constant in the last stage, probably as the result of terminal infection.

Course and Prognosis.—Some cases appear to run an acute course. We have seen cases which have died within three or four months of coming under observation, but there is always some doubt as to the previous history of the illness. Some apparently acute cases are really the acute termination of a chronic condition. The usual course of the disease is a chronic one. The duration varies considerably. The febrile cases are not likely to live more than a year, and death in any case is likely to take place within three years. Long remissions of symptoms, however, sometimes occur, and pressure symptoms may disappear.

We can recall a case in which there was pressure on the right lung causing collapse, and pressure on the superior vena cava. These symptoms entirely disappeared, and at a later date enlarged glands made

their appearance above the left clavicle. One of these was excised and the diagnosis was confirmed by the microscope. At a still later stage these glands in their turn disappeared also.

In another case there was obstruction of veins and phlebitis in the left leg, but these symptoms all cleared up.

Death may be due to an intercurrent affection such as tuberculosis or pneumonia. Pressure on the trachea or vital organs is said to be the most usual termination, but in our experience death from asthenia or intercurrent affections is more common. In the absence of these contingencies the patient may become very anæmic and cachectic, and finally die from asthenia.

Diagnosis.—It appears that out of a mass of conflicting evidence there now stands out with some degree of clearness a definite condition with pathological features as described by Greenfield, Andrewes, Reed and Longcope, and it is the condition which we have kept in view in the foregoing description. In dealing with symptoms we have mentioned the conditions which may be confounded with local manifestation of lymphadenoma. We have now to discuss the diagnosis in a more general way. The first essential in the diagnosis is to make a satisfactory examination of the blood. The positive evidence in favour of lymphadenoma may not amount to much, but a whole host of other conditions may be excluded.

The conditions which have to be distinguished are as follows:—

1. *Tuberculosis.*—The distinction between this and lymphadenoma may be extremely difficult. Sternberg regards lymphadenoma as a special form of tuberculosis, and we must confess that of all the cases we have seen diagnosed clinically as lymphadenoma and afterwards come to the post-mortem room, a larger number have been tuberculosis or lymphadenoma complicated with tuberculosis than pure lymphadenoma. A large number of cases diagnosed clinically as lymphadenoma are found to be tuberculosis when injections of the glands are made into guinea-pigs. On the other hand, the number of negative inoculations is too large to be ignored. A von Pirquet or Koch test, if negative, would be of some value in excluding tubercle. A positive reaction would not necessarily exclude lymphadenoma, since the two conditions are so often combined. An actual lymphocytosis is in our opinion much more likely to be indicative of tuberculosis than of lymphadenoma. Excision of a gland makes the diagnosis clear if the gland in question happens to be typical of either condition, or if

tubercle bacili can be demonstrated, but we have often found it necessary to examine many specimens before an opinion could be given even on post-mortem specimens. Our own practice is to excise a gland in every doubtful case, where this can be done with safety, to examine one portion histologically and to make inoculations with another. We have seen numerous cases in which a diagnosis would have been impossible without the use of this method. The temperature chart will in time help to distinguish the conditions. Tuberculosis does not show the severer forms of fever found in lymphadenoma unless there is septic infection. If there be septic infection the blood will show increase of fibrin and absence of eosinophilia, neither of which is found in lymphadenoma.

2. *Malignant Disease.* — Difficulty in differential diagnosis often arises, especially in the case of primary malignant disease in the mediastinum or retroperitoneal region, and also in cases of metastatic affection of glands when a primary tumour is not obvious. There may be just as much difficulty in distinguishing between lymphosarcoma and lymphadenoma running an acute course as there is in distinguishing between tuberculosis and the commoner variety of lymphadenoma. In some of the cases of acute lymphadenoma the leucocytosis and eosinophilia is greater than that usually seen in malignant disease. In some cases of generalised lymphosarcoma there may be an increase of white cells with a high percentage of lymphocytes. The temperature changes of lymphadenoma will probably be a serviceable diagnostic symptom in most cases of doubt. In lymphosarcoma the glands usually become confluent and form large masses, and there may be invasion of surrounding tissues, while in lymphadenoma the glands remain separate. The occurrence of remissions would favour the diagnosis of lymphadenoma rather than malignant disease. Whenever possible a gland should be excised for microscopic investigation.

3. *Leucocythæmia.*—The diagnosis can be made quite readily from the blood examination.

4. *Aleukæmic Leukæmia.*—We confess to a difficulty in understanding what this monstrosity of pathological nomenclature may mean, in spite of the prolixity of writers on the subject. If we take it to be early leukæmia, before there is any glandular enlargement, then there is no reasonable likelihood of it being confused with lymphadenoma. If leukæmia is associated with glandular enlargement we should find the usual blood changes, since the glandular enlargement is secondary to the blood condition.

5. Local glandular enlargement due to inflammatory processes, syphilis, filariasis, etc., may give rise to difficulty. In inflammatory conditions there is usually an obvious cause. Febrile syphilis may closely resemble lymphadenoma. The diagnosis will be determined by the history, the Wassermann reaction or the luetin reaction of Noguchi, the incidence of other symptoms of syphilis, and the effect of treatment. Filariasis will be distinguished by the examination of the blood and of the gland juices.

Treatment.—The patient should lead an open-air life as long as his strength permits. He should have good food up to the limits of his digestion. Arsenic seems to benefit symptoms. Very striking benefit has followed the exhibition of some of the organic preparations of arsenic, and we have seen cases in which symptoms disappeared in the course of a few days after an injection of salvarsan. No permanent cure has ever been recorded. Surgical interference seems to be useless, and in some cases one gets the impression that the growth of glands has been more rapid about the seat of operation than before.

In 1911 we published a case which is of great interest because of the striking temporary improvement produced by the intravenous injection of salvarsan (0·6 grm.). The patient had for some months suffered from the undulatory relapsing type of fever—ten days' fever, culminating on the fifth or sixth day at 103°, followed by ten days of normal temperature, and then again by fever, and so on. At the end of one of the febrile attacks the temperature continued high. An injection of salvarsan into the buttock caused very slight improvement for a day or two, but the fever went on, the patient emaciated, and was obviously sinking. An intravenous injection at the end of a month of this brought down the temperature to normal with startling suddenness, and it stayed down for more than a month. The glands, which had been swollen, soft, and tender, shrank and became hard and almost invisible, and the general improvement may be gauged by the fact that he gained 10 lb. in weight, and walked out of hospital to go to the country. Soon after, however, the fever returned. Subsequent intravenous injections of salvarsan always brought down the temperature and reduced the size of the glands, but for successively shorter periods. An intramuscular injection had no effect.

In several subsequent cases we have tried salvarsan, always with benefit. In one case, a child aged 9, in which the diagnosis had been confirmed by microscopic examination of an excised gland, the lympho-

mata entirely disappeared after two injections with an interval of a month. In another case with enlarged mediastinal glands as revealed by X-rays, and enlarged superficial cervical glands (examined microscopically), a complete return to normal followed the use of salvarsan.

Our present practice is to give salvarsan intravenously as soon as the diagnosis is made, and repeat it at regular—say, three-monthly—intervals for a year or two.

Both in estimating the effect of treatment and the likelihood of success in it, it is very important to remember that enlargement of superficial glands in the neck, axilla, and groin may be merely the termination of a process which has begun in internal glands, and not, as is too often assumed, a primary enlargement. A minute examination of the chest and abdomen should be made in every case, and radiography is often very helpful, especially in the chest. We have seen very few cases at so early a stage that the glandular enlargement in neck or axilla was not already associated with the presence of masses, large or small, in the mediastinum.

Literature

A full list of references is given by Ziegler, *Hodgkinsche Krankheit*, Fischer, Jena, 1911. See also *Practitioner*, 1911.

References to bacteriology are given in the text.

CHAPTER XXIII

MULTIPLE MYELOMA

MULTIPLE myeloma was first described by Kahler in 1889. The disease consists in the formation of tumours (either circumscribed or diffuse) in the bone-marrow, associated with pain and often with deformity, and in a large proportion of cases with the occurrence of a peculiar protein in the urine.

Etiology.—Cases have occurred at all ages between twenty-four and seventy-two, but it is most common between the ages of forty and sixty. Trauma has been suggested as a causal factor in a few cases, but it is difficult to exclude the probability that the injury merely attracted attention to the illness.

Pathology.—The bones most commonly affected are the ribs, sternum, cranial bones, and the vertebræ. The long bones are less frequently involved. The tumours are usually circumscribed masses, but diffuse infiltration also occurs. They may be of any colour from white to brownish red. Their consistency is usually rather greater than that of the marrow. The tumour growth may lead to rarefaction of the bone and spontaneous fracture may result.

Microscopically the picture is an active proliferation of one or other of the types of cell found in the marrow. The growth presents the general characters of sarcoma, but while its aggressiveness towards the marrow is very great, it shows little tendency to involve neighbouring structures, and does not invade blood-vessels.

As regards finer structure the tumours are not the same in all cases, and the following have been distinguished:—

1. Lymphocytoma.
2. Myeloblastoma.
3. Myelocytoma.
4. Plasmacytoma.

In addition to these Ribbert has described a case as erythroblastoma, but, so far, this is an isolated observation.

Symptoms.—The first symptom noticed is either the presence of a tumour or the occurrence of pain. The latter is always prominent, and may lead to a mistaken diagnosis of rheumatism. It is often associated with tenderness. The tumour growth may lead to great deformity. There is sinking in of the chest and great kyphosis, and it is commonly remarked that the patient's stature decreases. Spontaneous fractures of ribs and even of long bones have occurred. There is a loss of appetite, and as the disease progresses there may be marked cachexia. Fever is an occasional symptom. In some cases there is moderate enlargement of the spleen and lymphatic glands.

There is always some degree of anæmia. Hæmoglobin may fall as low as 15 per cent. In a few cases normoblasts and megaloblasts have been found in the blood. There is no constant change in the number or proportions of the white cells. In a few cases there has been rather a high percentage of lymphocytes, and myelocytes have occurred.

In rather less than 50 per cent. of cases there occurs a special protein (Bence Jones' albumose) in the urine. This substance coagulates when heated to between 40° and 60° C. and passes into solution again when further heated. Dissolved in salt solution, etc., it gives the typical reactions of albumose.

Nervous symptoms may develop. Subjective sensations such as headache and loss of memory are common. Hyperæsthesia may occur, and there is progressive diminution of reflex response to stimuli. Owing to tumour formation and deformity there may be compression-myelitis with corresponding symptoms.

Course.—The condition is progressive in the great majority of cases. In Kahler's case there were long remissions. The average duration of the illness is about one year, but the disease may end fatally in as short a time as six weeks or may last for eight years. Death results from cachexia and exhaustion, from pressure by the tumours, or from intercurrent affections such as hypostatic pneumonia.

Diagnosis.—In typical cases with pain, deformity and tumours, spontaneous fractures, cachexia, and anæmia the diagnosis is easy. In atypical cases it may be difficult or impossible. During life the condition cannot be distinguished with certainty from other forms of skeletal tumour (chondrosarcoma, myelosarcoma, or endothelioma).

The presence of Bence Jones' albumosuria tends to confirm the diagnosis in typical cases, but it must be remembered that it is very

frequently absent and that it occurs in a few other conditions. Thus its presence has been noted in myxœdema, lymphatic leukæmia, gastric carcinoma with bone-marrow metastases, toxic nephritis, and in one case, after amputation of the leg.

Examination by the Röntgen rays may aid in diagnosis. The bones appear somewhat rarefied but the tumours are shown as multiple dark masses.

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CHAPTER XXIV

HÆMOPHILIA

Definition.—A disease, usually congenital, characterised by a tendency to hæmorrhage, either spontaneous or associated with wounds.

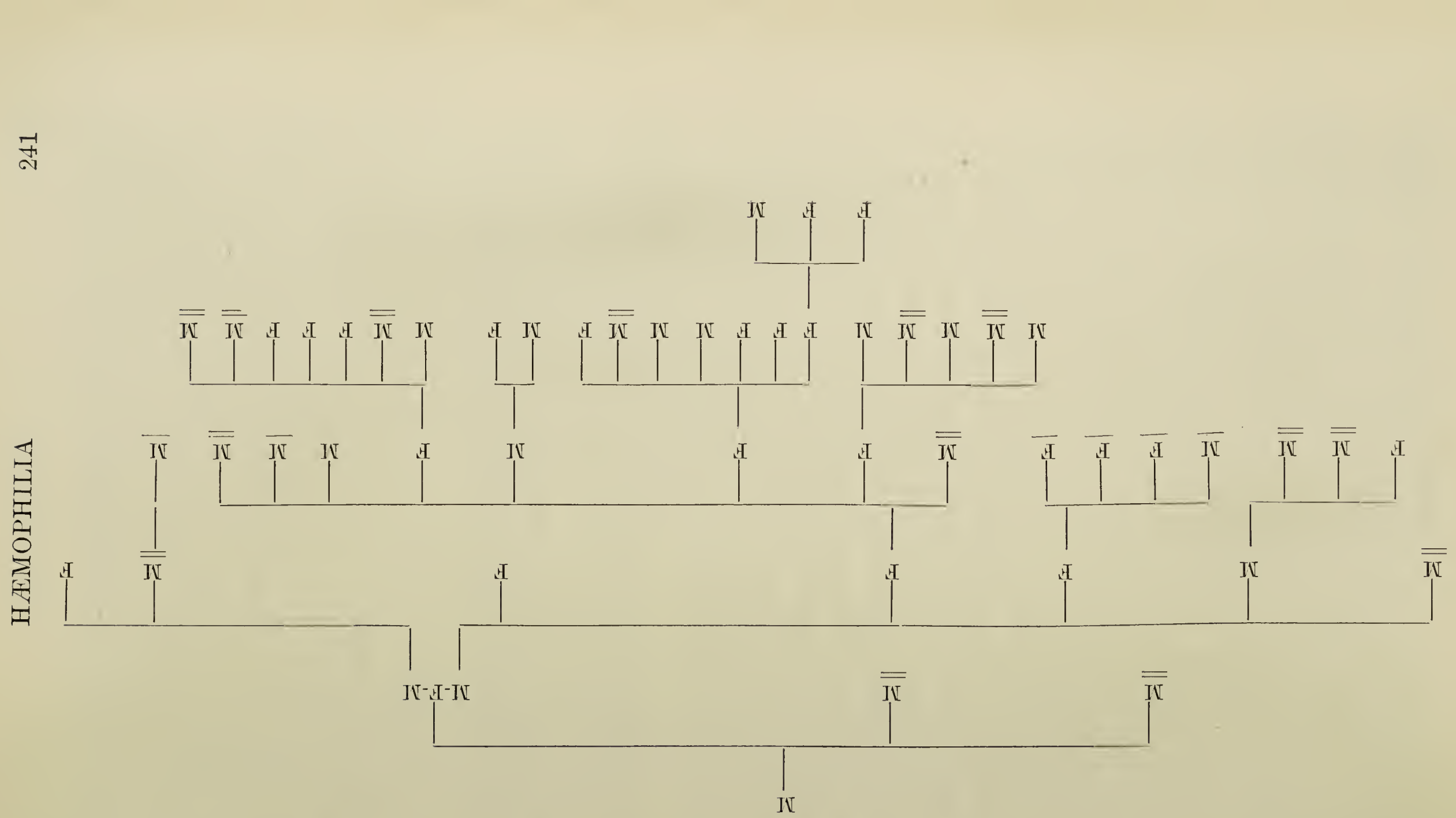
Etiology.—The disease is congenital in the great majority of cases. It must probably be admitted that *de novo* cases occur. We have certainly seen cases in which no family history could be obtained, but in some cases it is not possible to get a family history of any kind, and another difficulty arises from the fact that the congenital tendency may pass over several generations and break out again. The tendency is generally found in the male sex, and doubt has been expressed whether true hæmophilia ever occurs in the female. The condition may, however, be definitely stated to occur in females, and one female case has come under our own notice.

Fränkel and Bohm publish a table of 151 cases recorded as occurring in women. In twenty-nine of these the bleeding was on no occasion from the genital tract.

The hereditary transmission and the sex incidence of the condition are remarkable. The disease usually affects men, but the tendency to the disease is transmitted through the female line. Exceptions to this rule occasionally occur. The tendency has been transmitted from father to son although the mother was healthy and came of a non-hæmophilic stock, and the tendency has been transmitted through the father although the father himself had escaped the disease. Another remarkable fact regarding hæmophilics is their fecundity. Several genealogies have been published which trace the disease through as many as seven generations. We give two genealogies, one fairly typical, for which we are indebted to Dr. T. Y. Finlay, and a curious atypical history which came under our own notice.[1]

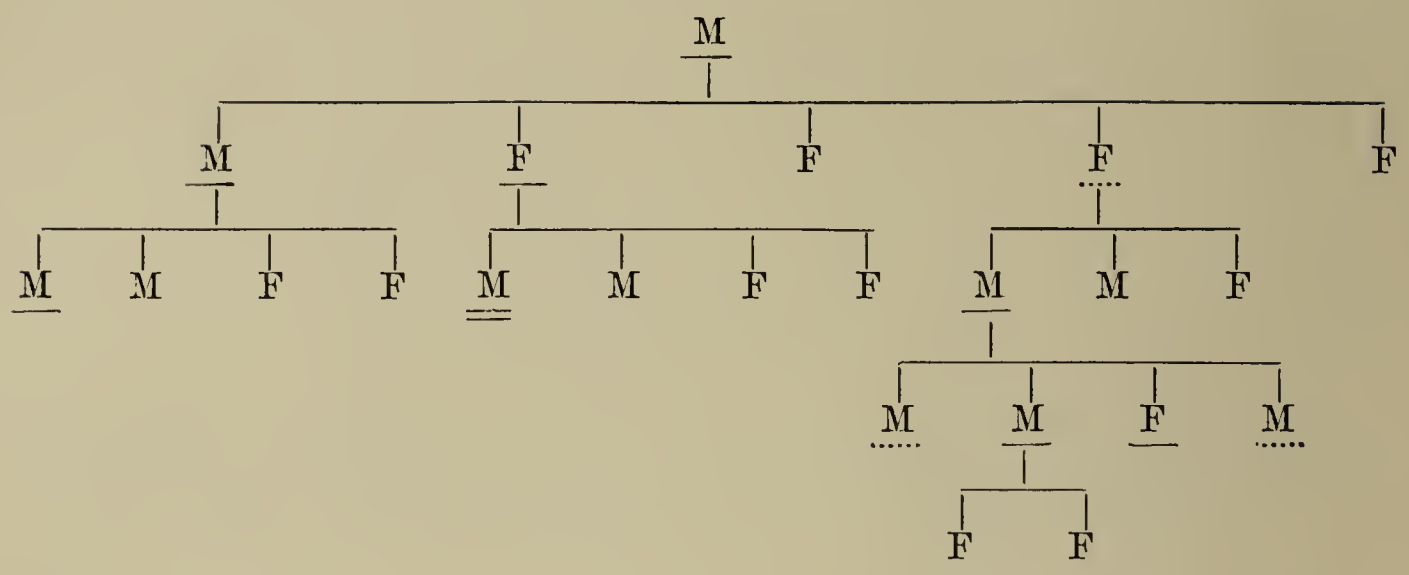
[1] Bulloch and Fildes give over 200 "typical" histories.

HÆMOPHILIA



GENEALOGY I.

GENEALOGY II.



In each case the letter M indicates a male, F a female. In no case was there intermarriage with a hæmophilic stock. The female of the second generation in Genealogy I. was married twice and gave birth to hæmophilics by both husbands.

A single line under the letter denotes symptoms of hæmophilia; a double line indicates that the person died of hæmophilia; the dotted lines indicate a slight degree of hæmorrhagic tendency.

The disease rarely shows itself before the first twelve months of life have elapsed. This is probably to be explained by the amount of care which usually surrounds the infant before that age. At the same time it is quite likely that many cases of hæmorrhage occurring either immediately or three or four days after birth are of this nature, and cases have occurred in which hæmorrhage soon after birth has been followed by symptoms of hæmophilia in later life. Addis quotes Nacke of Kirchheim as stating that he could usually say at birth which members of the well-known bleeder family, Mampel, would be hæmophilics, from the bleeding which took place from the cord even after it had been firmly ligatured. Several members of the family had died of such hæmorrhage. Care must be taken to exclude cases of hæmorrhage from the cord due to sepsis. In many instances there is a distinct tendency to improvement in the symptoms any time after the adolescent period. In several cases in our experience the tendency has entirely died out after the age of twenty, thirty, or forty.

Race seems to have no special influence, although it has been stated that Jews are specially liable to hæmophilic symptoms. It is possible that the rite of circumcision may reveal the tendency in Jews at an unusually early age. Social condition does not seem to have any influence on etiology. Cold and damp surroundings seem to favour the incidence of hæmorrhagic symptoms.

Pathology.—Apart from changes directly due to hæmorrhage, there is no demonstrable structural lesion to account for the disease. Undue thinness of vessel walls and a disproportion between the sectional area of the vessels and the volume of blood are among the conditions which have been regarded as causal conditions, but these views have been discarded by almost all recent writers. There is a general consensus of opinion that the main factor in the production of the disease is a diminished coagulability of the blood. This is regarded as the sole cause by most recent observers, but an undue friability of the capillaries is regarded as an additional factor by some writers. There can be little doubt that friability of the capillaries is a cause of hæmorrhage, and in some people bruising is very easily produced although the coagulability of their blood is normal. But Morawitz and Lossen have given strong evidence that friability of capillaries is not greater than usual in hæmophilics. They connected a cupping-glass with a mercurial manometer and noted the amount of negative pressure which was necessary in order to produce bruising in normal persons and then found that just as much suction was necessary to produce bruising in the subjects of hæmophilia. It seems a little difficult to conceive the amount of damage that may be done to capillaries in the course of moderate exertion and exposure to slight external violence if the bruising that occurs in hæmophilia may be taken as an index of the damage. We have in view the case of a young hæmophilic who persisted in indulging in dancing, and who was invariably covered with bruises as a result. At the same time it seems probable that moderate injury does cause rupture of capillaries, and that in healthy persons the rupture is sealed up almost at once by coagulation of the blood, while in hæmophilics the rupture is followed by a variable and frequently considerable amount of hæmorrhage.

Before discussing the different theories of the pathology of hæmophilia in more detail it may be desirable to give a brief résumé of modern views on the coagulation of mammalian blood in health.

Coagulation of the Blood.—The researches of Morawitz and Mellanby have done much to throw light on this subject.

When blood clots a soluble constituent of the plasma (fibrinogen) is split up into an insoluble substance (fibrin) and a small amount of another (soluble) globulin. The fibrin occurs in the form of threads, which contract and entangle the corpuscles, thereby forming a "clot." This clot contracts and from it there exudes a clear straw-coloured fluid (serum).

Solutions of fibrinogen do not coagulate spontaneously. A substance known as *thrombin* is necessary to bring about coagulation. This substance

is often called fibrin ferment, but the name is unfortunate, since it acts quantitatively, *i.e.* a measured quantity will bring about the coagulation of a definite quantity of fibrinogen and no more. Now thrombin, as such, does not exist in the circulating blood, but is evolved after blood has been shed. It is derived from the interaction of three other substances—(1) prothrombin, (2) thrombokinase, and (3) calcium salts.

1. *Prothrombin* (thrombogen, Morawitz; plasmozym, Fuld) is a substance present in circulating blood. It is always associated with fibrinogen in whatever way the latter has been obtained, and the amount of prothrombin is always proportional to the amount of fibrinogen. Prothrombin is in a condition of "adsorption" in the fibrinogen molecule, and the only way in which a solution of prothrombin can be obtained free from fibrinogen is to coagulate the fibrinogen by the addition of pre-formed thrombin. Fibrin is then precipitated and the fluid which exudes contains prothrombin, a substance which has no coagulating power except in the presence of thrombokinase and lime salts.

2. *Thrombokinase.*—Thrombokinase is not found in the circulating blood plasma. It is, however, present in the formed elements of the blood and in the tissues generally, especially in those rich in nucleo-protein. The greater the quantity of thrombokinase added to the blood the more rapid is the formation of thrombin from prothrombin. Certain authors have regarded foreign bodies, etc., as essential "thromboplastic agencies." But it has been shown by Cramer and Pringle[1] that the supposed influence of such agencies is really due to the blood-plates. If blood-plates are entirely removed by passing oxalate plasma through a Berkefeld filter no clotting occurs on the addition of calcium chloride. Blood caught in paraffined tubes does not clot, because the plates are not disintegrated as they are when brought into contact with glass.

3. *Calcium salts* are also essential for the formation of thrombin. They have a much more powerful action than salts of the other earthy metals, so that their action is specific rather than ionic. They have also an action in breaking up blood-plates and thus liberating prothrombin.

Although thrombokinase and lime are essential for the formation of thrombin, they are not required in the process of clotting after thrombin has been formed.

Antithrombin.—In plasma there is a substance which antagonises the clotting action of thrombin. When tissues are wounded thrombokinase is liberated and in its presence the prothrombin with the lime salts forms thrombin. Thrombin, having a close affinity for fibrinogen, quickly forms fibrin, before the thrombin can be antagonised by the antithrombin. Most of the thrombin is precipitated with the fibrin. Any fresh blood that finds its way into the clot is coagulated by the thrombin and prothrombin is set free, but if no more thrombokinase reaches it no more thrombin is formed. That part of the thrombin which is not precipitated with the fibrin is gradually neutralised by the antithrombin.

[1] *Quart. Journ. of Exper. Physiol.*, vi. 1913.

To summarise:

Thrombokinase causes the union of { *Prothrombin* and *Lime Salts* } to produce *Thrombin*.

Thrombin converts fibrinogen into fibrin.
Antithrombin inactivates excess thrombin.

Howell interprets the interaction of these substances rather differently. He holds that prothrombin may be converted to active thrombin by the action of lime alone. This activation does not occur in the circulating blood, because antithrombin is present in sufficient amount to prevent the reaction. In shed blood the tissue cells or blood-cells and plates furnish a thromboplastic substance which neutralises the action of the antithrombin and thus permits the calcium to react with the prothrombin to form thrombin, which in turn reacts with fibrinogen to form fibrin.

Sahli regards hæmophilia as a cellular anomaly both of the blood corpuscles and of the endothelial cells. Blood does not coagulate readily, because there is a deficiency of thrombokinase in the blood and vascular endothelium. A clot may form when extravasated blood comes in contact with the tissues where there is thrombokinase, but in spite of this clot bleeding may continue because no clot forms in the ruptured vessels themselves. Normal blood corpuscles have a powerful action in increasing the coagulability of hæmophilic blood, although hæmophilic corpuscles have much less effect.

Morawitz and Lossen ascribe hæmophilia to a deficiency of thrombokinase in the tissues in general, and find that the addition of thrombokinase to hæmophilic blood causes a rapid coagulation.

Weil describes two forms of hæmophilia, a family form and an accidental or sporadic form. In the former he holds that the essential pathology is an excess of antifibrin ferment (antithrombin), and in the latter he considers that the error consists in a deficiency of the constituents of thrombin.

Nolf and Herry consider that the interaction of fibrinogen, prothrombin, and thrombozyme (thrombokinase) with lime gives origin to fibrin and thrombin. Thrombozyme is not found in tissues generally but is abundant in leucocytes, blood-plates, and vascular endothelium. The blood thus contains all the elements necessary for the formation of clot. It remains fluid in the vessels because the liver produces antithrombin, and in normal conditions there is an equilibrium which maintains fluidity. In certain intoxications the liver may secrete this antithrombin in great excess, but this is not a factor in producing hæmophilia. The cause of hæmophilia is the functional insufficiency

of thrombozyme. The vascular endothelium plays a large part in secreting thrombozyme, and along with this deficiency there is an associated friability which accounts for the many slight accidental hæmorrhages in hæmophilia which are not accounted for by mere incoagulability of the blood.

Addis finds that coagulation time is delayed, and that the fault lies in the slow formation of thrombin rather than in the interaction between thrombin and fibrinogen once thrombin has been formed. The rate of formation of thrombin in hæmophilia is unduly slow. He could find no evidence of the presence of any substance inhibiting coagulation. It is not possible to obtain as short a coagulation time in hæmophilic as in normal blood by the addition of any amount of calcium. When large amounts of thrombokinase were added the coagulation time in both normal and hæmophilic blood became very rapid. When only small quantities were added the characteristic delay in the case of hæmophilic blood again became evident. When the amount of thrombokinase in normal and in hæmophilic blood was compared there was no difference. A deficiency in thrombokinase is therefore not the cause. There was no quantitative deficiency of prothrombin but a qualitative difference was found, inasmuch as it showed a very slow rate of change into thrombin in the presence of calcium and thrombokinase. It was found that the addition of a very small quantity of normal prothrombin greatly accelerated the coagulation of hæmophilic plasma, whereas the addition of an equal quantity of hæmophilic prothrombin had no effect. Addis therefore ascribes hæmophilia to an inherited anomaly in the construction of the prothrombin of the blood which reveals itself in the unduly long time required for its activation.

Addis's researches go far to explain some of the curious phenomena of the disease, such as the occasional persistence of bleeding from a small wound and comparatively slight hæmorrhage from a larger wound, and the fact that bleeding frequently continues although a clot may be present. When a wound is made blood escapes and fills the cavity. Thrombokinase from the injured tissues mixes with the blood which is in contact with the sides of the wound. A layer of fibrin may thus be deposited on the sides of the wound, but in the more centrally situated blood the concentration of thrombokinase is not so great. Owing to the delay in the formation of thrombin this part of the blood is driven out of the wound before sufficient thrombin has been formed to coagulate it. It must be remembered that thrombin acts quantitatively, and that although a small quantity may pass from the periphery of the wound

towards the centre, it may cause a mere partial loose coagulum through which blood may trickle, washing away any thrombokinase (which now reaches it with difficulty through the fibrin layer over the surfaces of the wound) before it has time to convert the prothrombin into thrombin.

We consider that delayed coagulability of the blood is probably the sole factor, and is certainly the most important factor in the production of hæmophilia, and that in our opinion the most convincing view of the cause of the delayed coagulability is that of Addis.

Symptoms.—The subjects of hæmophilia are usually fair, with good complexions. The muscles are generally not powerful, and there is a fair but not excessive development of subcutaneous fat.

Prodromal Symptoms.—Prodromal symptoms have been described in many instances as indicating that a hæmorrhage was imminent. Symptoms of plethora, headaches and palpitation, and a sense of tightness have been described in this connection. Such symptoms are exceedingly rare. We can recall one case occurring in a student of medicine who assured us that he could always foretell an attack of hæmorrhage (usually epistaxis) by a feeling of special "fitness" for a few days previously.

Hæmorrhagic Symptoms.—The hæmorrhagic symptoms may conveniently be divided into external, internal and interstitial, and synovial.

External Hæmorrhages.—The external hæmorrhages may be spontaneous but are more usually associated with wounds. By far the most common spontaneous hæmorrhage is epistaxis. According to Grandidier the next most common sites in order are the gums, stomach, intestines, urethra, and lungs. Much less common are hæmorrhages from the skin of the head, tongue, finger-tips, tear-papilla, eyelids, external ear, vulva, umbilicus, and scrotum. Most female hæmophilics do not suffer from excessive hæmorrhage in connection with menstruation and parturition, but in some cases the former function leads to a degree of anæmia which is barely recovered from before the next period is due.

Traumatic hæmorrhages are specially dangerous in hæmophilia. Fatal bleeding has followed the extraction of a tooth or circumcision. Long-continued hæmorrhage may follow trivial scratches, and a shaving cut is a contingency which may play havoc with morning engagements. We knew a hæmophilic farmer who for this reason always shaved on

the evening before a market-day. The bleeding is a capillary oozing, which may persist for hours or days. It may continue in spite of the formation of large masses of clot, and in connection with epistaxis and bleeding from other mucous surfaces large loose adherent clots commonly occur. These may decompose and give rise to great discomfort.

Punctures into the skin do not bleed unduly freely owing to the sealing of the wound by the elasticity of the tissues. In taking samples of blood for examination it is better to puncture the finger than the ear, and in severe cases it might be well to use a round needle instead of one with cutting edges. Puncture of a vein is also a safe proceeding, as the elastic wall at once retracts and closes the wound made by a small needle.

A curious fact is the varying liability to hæmorrhage at different times. At one time slight pressure with a finger may be followed by a large ecchymosis, while a week later a much more severe injury seems to have no specially bad effect.

Internal Hæmorrhage. — Petechial hæmorrhages are not common. Very extensive effusions may occur in connection with slight pressure. Muscular action may be sufficient to cause hæmorrhage. Large hæmatomata may result and may be absorbed in time, but instances have occurred of calcification of the effused blood. Along with the effusion there may be great pain, and paralysis of nerves may result. Blood may be effused into the stomach and bowel, and the presence of large decomposing clots may lead to marasmus and death. Hæmorrhage in the serous sacs and into the meninges is rare. A few cases of fracture of the long bones in hæmophilics have been reported. There is very great swelling and the temperature rises. There seems to be no delay in union.

Joint Hæmorrhages.—Any joint may may be affected. The order of frequency with which the joints are affected is knee, ankle, wrist, elbow, hip. The swelling comes on suddenly and is always associated with pain. As a result of the hæmorrhage and tension there may be inflammation, and the effused fluid blood gives rise to fluctuation. The temperature rises and a mistaken diagnosis is readily made. The future history of the joint varies. The effused blood may rapidly disappear. There may be repeated serous or hæmo-serous effusions. Arthritis is a common sequel, and in such a case the clot is specially liable to become organised by fibrous tissue passing in from the synovial membrane and the joint may undergo firm fibrous anchylosis. Lipping of the joint and erosion of the cartilage may occur, leading to a condition

of arthritis deformans. Volkmann's contracture is sometimes a sequel of joint injury.

Blood Changes.—Apart from the delayed coagulation time there is no change. The number of red corpuscles, white cells, and plates shows no abnormality until hæmorrhage has given rise to anæmia. Owing to the gradual and prolonged nature of the hæmorrhage leucocytosis is not often noticed. The proportions of the leucocytes are not altered. In one of our cases which ended fatally from epistaxis and bleeding from the gums the red cells on the day before death numbered 295,000 per c.mm., the leucocytes numbered 4400, there were 64 per cent. of polymorphs and a few normoblasts.

Diagnosis.—Perhaps the family history is the most important diagnostic criterion. Another important point is that the hæmorrhage is generally associated with trauma. Even in the so-called spontaneous hæmorrhages it will be found that it is hardly possible to exclude the possibility of some force having been applied to the seat of hæmorrhage. This point will serve in many cases to distinguish the condition from purpura, in which the hæmorrhages are usually multiple and occur in many instances in sites which are not likely to have had pressure or violence applied to them. A diminished coagulability of the blood favours the likelihood of hæmophilia.

Mistakes are most likely to arise in connection with the joint affections, more particularly as the condition is rare. It is important from the point of view of treatment that a hæmophilic joint affection should not be overlooked. On the other hand, a mistaken diagnosis of hæmophilia in a case of recurring epistaxis or hæmaturia will have no ill effect upon the patient, although in course of time it may affect the reputation of the practitioner.

Prognosis.—This is always grave, especially in young subjects. After early childhood the risk is less, possibly because the child's attendants have learned to take special care; but there is often a real diminution in the bleeding tendency. The outlook is more serious in boys than girls. Grandidier states that of 152 boy hæmophilics, 81 died before the termination of the seventh year. In most cases the tendency diminishes as age advances, and in many of the surviving cases it has disappeared by the age of twenty or later. On the other hand, patients with marked hæmophilic symptoms have reached

mature age with the tendency persisting. Menstruation and parturition do not add greatly to the risk to life in the great majority of cases, but in a few cases menstruation is a source of recurring anxiety.

Treatment.—*General.*—Hæmophilic children must be watched with great care, in order that even minor accidents may be avoided. Teachers and others in charge of such children should be warned of the existence of the condition. Charges against teachers of excessive corporal punishment in the case of hæmophilics are by no means unknown.

The choice of occupation is, of course, considerably restricted. Dentists and doctors should be informed of the existence of the tendency in the patient or in any of the members of the family. Females of a hæmophilic stock should be advised not to marry. This also applies to male bleeders. The more remote possibility of transmitting the disease may be pointed out to non-hæmophilic males of a hæmophilic stock, the actual risk in such cases being determined by a survey of the whole family history.

In hæmophilia the bowels should be carefully regulated, and articles of diet or luxury which have any tendency to cause disturbance of the vascular system should be used only with the greatest care. Residence in warm climates seems to lessen the tendency to bleed in some cases.

Medicinal Treatment. — Calcium salts have been strongly recommended, but probably on insufficient grounds. In estimating the effect of remedies the tendency of the symptoms to vary from time to time has to be remembered. Addis has demonstrated that the amount of calcium which can be added to the blood is less than the amount necessary to affect coagulation. At the same time it can do no harm, and Wright has strongly recommended a mixture of equal parts of calcium lactate and magnesium carbonate, checked by observations on the coagulability of the blood. Wright has also advocated the inhalation of carbon dioxide.

Gelatine (5 per cent.) injections have been tried, but reports on its efficacy are contradictory, and in some cases toxic symptoms have followed its use, as well as disasters from imperfect sterilisation. Gelatine can be administered without danger by the mouth, and benefit has been alleged to follow its use.

Grant, arguing from the rarity of the condition in females, administered ovarian extract with beneficial effect in one case. Among a host of other substances which have been employed are raw meat juice, thyroid

extract, ergot, adrenalin, turpentine, perchloride of iron, and practically all the drugs which have any styptic effect.

Serum Treatment.—There is fortunately a consensus of opinion, even among those who differ regarding the explanation of the delayed coagulation time, that benefit results from serum treatment, which was introduced by Weil. Fresh serum from the horse, rabbit, or man may be used. Ox serum should not be employed, as it may cause severe symptoms of headache, vomiting, rigors, and cyanosis. The serum may be given by the mouth, but is more effective when administered hypodermically or intravenously. The latter method is to be preferred as being more efficacious. The injection can be made into a vein without any damage to tissues, and the puncture is sealed by the elasticity of the tissues, while a hypodermic injection almost invariably leads to ecchymosis or the formation of a hæmatoma. The dose of serum is 20-30 c.c. hypodermically, or 10-20 c.c. intravenously. A reduction should be made in the case of children.

While fresh serum is always to be preferred when it is available, antidiphtheritic serum, or the horse serum which is now supplied by several firms, may be employed. It has been stated that even heated serum which contains no thrombin is of service. Weil holds that the effect of the serum lasts for about a month. Labbé recommends the intravenous injection of serum once a month, and says that by this means the coagulation time can be brought to normal and that surgical operations may then be performed with safety. Nolf and Herry, while agreeing that serum does good after it has been absorbed, suggest that even better results can be obtained by the use of propeptone. This substance has a double action, according to these authors. If injected rapidly it stimulates the liver to throw out a large amount of antithrombin, but if injected slowly this stimulation does not occur, but there is a greatly increased output of thrombozyme (thrombokinase) by the leucocytes and vascular endothelium. A subcutaneous injection of 10 c.c. of a 5 per cent. solution of Witte's peptone in 5 per cent. salt solution may be given on alternate days. This is said to give good results in cases of rebellious hæmorrhage from causes other than hæmophilia. The advantages of peptone in the matter of availability and in the ease with which it can be sterilised are obvious. The only danger in using it is the possibility that it may temporarily increase the severity of the condition which it is sought to check. So far as we know, Nolf and Herry's results have not been confirmed by other writers.

Local Treatment.—The ordinary measures for the arrest of hæmor-

rhage are of course indicated. The part should be put at rest, and if possible fairly firm pressure should be applied. The presence of loose clots in a wound or bleeding surface appears to do more harm than good, and there may be continued hæmorrhage from the centre of a wound which has a firm layer of fibrin attached to its sides. If oozing continues in spite of clots these should be removed, and the surface should be thoroughly soaked with a strong solution of thrombokinase, in the form of an extract of lymph gland, thymus, testis, or other source of nucleoprotein, made by chopping up the organ in 0·9 per cent. saline solution containing 1 per cent. of sodium carbonate. Probably thrombokinase from a human source is preferable when it can be obtained. Failing stronger solutions, fresh human blood may be used as a source of thrombokinase. A powerful extract of thrombokinase may be prepared by washing sheep's fibrin with tap water till it is free from hæmoglobin and then kneading about 20 grms. of the wet fibrin in 300 c.c. of distilled water (Buswell [1]).

Addis reports the case of a gradually increasing hæmatoma in which the bleeding was eventually stopped after incision and stripping away a firm film of fibrin from the wound surface and thereafter applying thrombokinase.

To sum up, we may say that the precautionary measures already discussed are indicated. The administration of lime may possibly do good and is not likely to do harm. Intravenous injection of fresh serum is perhaps the most efficacious treatment at present known. The injection of peptone appears worthy of further investigation. Ordinary local measures for the arrest of hæmorrhage should, if necessary, be supplemented by the removal of clots and the application of a solution of thrombokinase.

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CHAPTER XXV

PURPURA—SCURVY—INFANTILE SCURVY

Purpura

Purpura is a symptom rather than a disease. The condition is characterised by extravasations of blood into the skin, and, less commonly, by hæmorrhages from the mucous membranes. The extravasations into the skin are usually small spots about a millimetre in diameter (petechiæ); sometimes they are considerably larger (vibices), and sometimes they may occur over large areas (ecchymoses). They are at first bright red in colour, but fade through purple in a day or two and eventually become a dull brown colour. Sometimes they appear in successive crops, so that all stages are present at the same time. The spots do not disappear on pressure, and are thus easily distinguished from inflammatory eruptions.

In only a small proportion of the cases is the coagulation time of the blood increased, and even in these cases the diminished coagulability is to be regarded as incidental rather than essential. The essential lesion is an increased friability of the small vessels, possibly the small veins. The vessel weakness is probably a multiple local lesion, since the bleeding in purpura is spontaneous and traumatic bruising does not occur unless there is concomitant diminution of the coagulability of the blood.

Varieties.—It is impossible to give a satisfactory classification of the causes of purpura, and even when all the known causes have been mentioned there is still a considerable group of cases unaccounted for. The chief conditions associated with purpura are noted below, but it will be seen that the groups mentioned are not necessarily mutually exclusive.

1. *Morbid Conditions of the Blood.*—Purpuric lesions sometimes occur in cases of pernicious and secondary anæmia and in leucocythæmia, especially in the terminal stages of the chronic forms, and sometimes throughout the whole course of the acute cases. The extravasations

which occur in hæmophilia are not to be regarded as purpuric, since they are not usually spontaneous and appear to be solely due to a defect of coagulation.

2. *Toxic Conditions.*—(*a*) The most frequent cause of purpura is rheumatism. The extravasations are most common on the legs, less common on the arms, and rare on the trunk. The hæmorrhages are often associated with other lesions. A case not uncommonly begins with manifestations of erythema nodosum on the shins, and later, extravasations occur in connection with the lesions.

Schönlein's Purpura—Peliosis Rheumatica.—This condition is associated with a multiple arthritis, not infrequently a sore throat, and a raised temperature which may reach 103° F. The hæmorrhagic rash makes its appearance on the legs or about the affected joints, and may be the only skin affection, but more usually there are other associated skin lesions. The most common of these is urticaria, but vesicles may occur, sometimes erythema nodosum, and more rarely large patches of œdema. The urine is reduced in amount and may be albuminous. Some cases have been associated with chorea. Prognosis is good, but there is a tendency to relapses.

(*b*) Septicæmia in all its forms is often associated with purpura. Any of the exanthemata may show hæmorrhagic rashes, and the continued fevers and malaria may cause purpura.

(*c*) *Gastro-Intestinal Conditions.*—Absorption of intestinal toxins may give rise to purpura.

Henoch's Purpura.—This variety is most commonly seen in children. The purpura is often associated with other cutaneous lesions such as erythema. There are sometimes hæmorrhages from the mucous membranes. Attacks of abdominal pain, vomiting, and diarrhœa are common. A large number of cases have been recorded in which the purpura was associated with intussusception. There are sometimes slight pains or swellings of the joints. Unless associated with a grave abdominal condition prognosis is good, although a few fatal cases have been reported. Hæmorrhage, nephritis, and exhaustion are the special dangers. Relapses are not uncommon, the condition tending to recur for several years.

(*d*) *Cirrhosis of the Liver and Jaundice.*—Jaundice of temporary character is rarely if ever accompanied by purpura. The longer jaundice lasts the more likely it is to be accompanied by hæmorrhage, and therefore it is most common with malignant disease either of the liver itself or in such a position as to cause obstruction of the common duct. The

malignant cachexia also plays a part in its production. Purpura is not uncommon in the late stages of cirrhosis of the liver.

(*e*) Bright's disease in all its varieties and arteriosclerosis may be causes of purpura, as of other hæmorrhages.

(*f*) *Drugs and Poisons.*—The chief causes of purpura under this heading are iodide of potassium, chlorate of potassium, copaiba, belladonna, mercury and phosphorus, fungi, snake venom, and serum.

3. *Cachexia.*—This is a common cause of purpura. Among the chief conditions there may be mentioned debility from any cause, privation, congenital syphilis, tubercle, rickets, and malignant disease.

4. *Mechanical Conditions.*—Whooping-cough, heart disease, epilepsy, or any condition leading to great congestion may cause *orthostatic* purpura. Self-inflicted injury may lead to *purpura artifacta.*

5. *Morbid Conditions of the Nervous System.*—Purpura has been noted in association with locomotor ataxia, peripheral neuritis, myelitis, and hysteria.

6. *Unknown Conditions.*—Cases occur when none of the above or indeed any causal condition can be discovered.

Purpura Simplex.—This is a mild form common in children. A purpuric eruption, usually petechial, occurs on the lower limbs alone or on the limbs and trunk. There may be slight fever, loss of appetite, and anæmia. Diarrhœa sometimes occurs. Patients are usually well within a fortnight.

Purpura Hæmorrhagica—Morbus Maculosus (Werlhof).—This condition is one of severe purpura accompanied by hæmorrhages from the mucous membranes. It usually affects children in delicate health, and is more common in girls. Cases in adults have been reported. Initial symptoms are indefinite ill-health and weakness. Purpuric spots occur on the skin and increase rapidly in number and size. Bleeding from the mucous membranes begins. Epistaxis, bleeding from the gums, hæmatemesis, hæmaturia, and, less commonly, hæmoptysis may occur. The patient becomes rapidly and profoundly anæmic. A certain amount of fever is usually present. Cases may terminate fatally.

Diagnosis.—Malignant types of fevers, especially measles and small-pox, have to be distinguished by the history, the temperature, and by the examination of the blood. Scurvy is distinguished by the history, the condition of the gums, and the intramuscular hæmorrhages. It is of the first importance to exclude the true blood diseases by a proper blood examination.

Prognosis varies with the cause and severity of the condition. Cases of *purpura fulminans*, occurring especially in children, may be fatal within twenty-four hours, sometimes before there has been any bleeding from mucous membranes. This contingency, however, is fortunately rare, and even severe cases with multiple hæmorrhages, albuminuria, and pyrexia usually get well. In favourable cases the bleeding stops within a fortnight, but a much longer time may elapse before the anæmia is recovered from. There may be recurring attacks of epistaxis after other symptoms have disappeared.

The Blood Changes.—The blood changes are in no way characteristic. In mild cases there may be no demonstrable change; in others a marked anæmia may rapidly ensue, even when there has been no actual hæmorrhage from mucous membranes. These cases are not easily explained, since the amount of blood in the skin rashes is very slight, and is indeed hardly noticeable in transverse microscopic sections of the purpuric spots. In purpura hæmorrhagica the anæmia may be considerable, and the usual picture of secondary anæmia develops, varying in the usual way according to the degree of severity. The leucocyte count may show a considerable transient increase soon after the onset in the more severe cases. If the condition is severe or lasts for any time there may be a more persistent leucocytosis, and some myelocytes may appear in the peripheral blood. In the mild forms the leucocyte count is not altered greatly. In many cases of purpura simplex it tends to be rather low. Blood-plates are nearly always diminished.

Treatment.—If it can be discovered, the causal condition is to be dealt with. In all cases it is important to keep the patient at rest in bed. In the cases of unknown origin anti-rheumatic remedies may be tried, but are not as a rule particularly successful. In mild purpura in children arsenic sometimes appears to do good. Oil of turpentine has a special reputation in this condition. Calcium salts do no good. In cases where there seems to be a diminished coagulability of the blood the administration of serum, as in hæmophilia, might be worth a trial. Adrenalin has been successful in several instances. The results of hæmorrhage may require local treatment.

Scurvy—Scorbutus

Definition. — A disease characterised by great debility, a spongy condition of the gums, anæmia, and a tendency to hæmorrhages.

Etiology.—Sex and age have no special influence. The essential cause of the disease is deprivation of fresh vegetable food, fresh meat, and fresh milk. In past times it was the scourge of sailors on long voyages, but it has also affected armies in the field, and epidemics have occurred in prisons and even hospitals. In parts of Russia scurvy is endemic and occasionally becomes epidemic.

Sporadic cases are occasionally seen, but in these it is easy to obtain a history of an improper dietary. Such cases occur most often among the poor of large towns, especially in persons who live alone, and who from poverty or carelessness do not take a sufficiently varied diet. Old women living practically entirely on tea and bread and butter fall easy victims. Cold, damp, depressing surroundings and overcrowding are important accessory factors.

Pathology.—The morbid changes are usually well marked, but they are not specific. They are chiefly the effects of hæmorrhage into the skin, muscles, connective tissues, and internal organs. The gums show swelling and sometimes ulceration. There may be ulcers in the ileum and colon. The spleen is enlarged and soft. There are degenerative changes in the heart, liver, and kidneys.

The intimate nature of the disease is not yet understood. The symptoms have been ascribed to the lack of potassium salts. Another view is that they are due to the absence of salts of the organic acids, citrates, tartrates, and malates, leading to a diminished alkalinity of the blood. It is possible that in the absence of these substances acids derived from protein food-stuffs are not adequately neutralised, since prolonged starvation in itself does not necessarily cause scurvy. A different view of the disease is that it is due to a micro-organism, although no definite germ has been determined. In Russia the disease is very generally regarded as an infection.

Symptoms.—The disease begins insidiously. The patient suffers from weakness and indefinite pains, and there is increasing pallor. In about a week petechial spots make their appearance, generally on the legs, and always starting round the hair follicles. Larger hæmorrhages may occur and may cause swellings. There are often hard swellings in connection with the muscles owing to hæmorrhages between their fibres; these are most common in the calves. The gums become swollen, spongy, and may ulcerate and bleed readily. This change is only seen where teeth are present, and there may be portions of comparatively healthy

gum at parts where teeth are absent. The teeth often fall out. The breath is very fœtid. The appetite is impaired apart from the great discomfort in eating. The tongue is swollen, red, but not as a rule much furred. The salivary glands may be enlarged. Constipation is the rule; diarrhœa rarely occurs. Palpitation, feebleness, and irregularity of the heart are common; hæmic basal murmurs are usually present. Effusions into the serous sacs are not uncommon. The urine is often albuminous. Specific gravity is high. Phosphates are increased. Headache, mental depression and delirium may occur. Convulsions and hemiplegia have been described. Curious ocular symptoms sometimes occur. One of the most common is "night-blindness" (nyctalopia), patients being unable to see as soon as dusk begins; in other cases vision is not so good in daylight (hemeralopia).

Hæmorrhages may occur from any of the mucous membranes. Meningeal hæmorrhage sometimes occurs. Subperiosteal hæmorrhages, which may cause sloughing sores, and actual necrosis of bone are not uncommon. Old wounds may break down, and separation of the cartilages from the sternum and disintegration of callus in a recently repaired fracture have been described. Arthritic symptoms are sometimes severe. Fever is usually absent unless there be inflammatory complications.

The Blood Changes.—The blood changes are not characteristic; they are those of a secondary anæmia, of varying degree of severity. In the severer cases normoblasts and even megaloblasts may be seen. The leucocytes, owing to the hæmorrhages, are generally found to be increased, but in the absence of recent hæmorrhage or inflammation they are diminished. Blood-plates are diminished.

Course.—If the unfavourable conditions which induce the condition persist the outlook is very grave. Heart failure, sudden syncope, or exhaustion is a common termination. Pneumonia sometimes supervenes, and is ill-borne. Hæmorrhage is seldom serious. Unless the disease is very advanced it yields readily to treatment. Effusions, even when blood-stained, rapidly clear up, and other symptoms quickly disappear.

Treatment.—*Prophylaxis.*—Under Board of Trade regulations ships must carry an adequate supply of lime juice and other antiscorbutics, so that scurvy among sailors is now very rare.

Of the Disease.—The danger of sudden syncope must be guarded against by keeping the patient in bed for at least a week. Abundance of fresh vegetables and fruit speedily cures any case of moderate severity. In the more severe cases with gastric derangement, fresh milk and scrapings of meat may be given, with the addition of teaspoonful doses of lemon or orange juice. As the patient improves the diet should be more liberal, and plenty of green vegetable food and fruit should be insisted upon. The gums may be treated by the application of a solution of nitrate of silver or carbolic acid and the frequent use of antiseptic and astringent mouth washes. Other symptoms must be treated on general lines.

Infantile Scurvy—Barlow's Disease

Infantile scurvy arises from improper feeding. Proprietary foods, condensed milk, and even boiled milk appear to lack some antiscorbutic principle, so that children fed exclusively on these substances are liable to the disease. The essential lesion is subperiosteal hæmorrhage.

Symptoms.—The affected child begins to show indications of pain whenever it is moved. This pain is at first limited to the lower limbs, especially to the tibiæ, but in more severe cases the upper limbs are also affected. There is thickening around the shafts of the bones. There is often a certain degree of symmetry in the distribution of the lesions. There may be thickenings in connection with the scapulæ, and weakness of the back may be a noticeable feature. Crepitus between the shaft and epiphysis of the long bones can sometimes be elicited. Sometimes the sternum and a portion of the attached ribs may sink back as if they had been subjected to violence. There may be thickenings in connection with the bones of the skull and face. Proptosis may suddenly develop, with fulness and ecchymosis of the upper eyelid. The temperature is irregular. If teeth have appeared the gums may be spongy.

The Blood Changes.—There is always severe anæmia. A reduction of red cells below one million has been noted. The hæmoglobin shows a reduction to a rather greater extent than the red corpuscles. Nucleated red cells are not uncommon. The leucocyte count is usually increased, but the special blood-picture of young children must be borne in mind in interpreting the results of examination. Blood-plates are diminished.

Treatment.—Prophylaxis is important. Milk should not be steril-

ised by boiling unless some fresh meat extract or fruit juice forms part of the dietary, and children should not be fed exclusively or in large measure on proprietary foods. The disease is readily amenable to treatment. The diet should consist mainly of fresh cow's milk. A little fresh meat juice may be given with a small quantity of mashed potato. Small quantities of orange, grape, or sweetened lemon juice may be administered several times daily. The anæmia may require the usual treatment, and the affected limbs should be kept at rest by bandages and cotton-wool and suitable appliances.

CHAPTER XXVI

PAROXYSMAL HÆMOGLOBINURIA

A DISEASE characterised by the occasional passage of blood pigment in the urine.

Etiology.—The condition is more frequent in males than females, and usually affects young adults. A history of malaria has been obtained in some cases. More frequently there is a history of syphilis. There is a certain association with Raynaud's disease, especially in the milder forms of that condition. The attacks are usually determined by a chill, sometimes by active exercise. In predisposed persons washing the hands in cold water may bring on an attack.

Pathology.—The condition is generally believed to be due to a toxin in the blood. According to Donath and Landsteiner and to Eason the toxin acts as an intermediary body or amboceptor. It cannot by itself produce solution of red corpuscles. For this the addition of a thermolabile complement is required. The intermediary body anchors itself to the red blood corpuscles when they are exposed to a temperature lower than that of the body. *In vitro* the union takes place at 0° C. or at room temperature. The further combination of complement with the conjoined corpuscles and intermediary body does not take place at 0° C. but does so at room temperature, and hæmolysis results. *In vivo*, atmospheric cold and stasis of the peripheral circulation probably cause a reduction of temperature sufficient to permit of the union of intermediary body and red corpuscles. (This probably accounts for the connection with Raynaud's disease.) The further union of complement probably occurs most rapidly when the blood returns to the central organs. Eason holds that the serum at all times contains enough potential toxin to cause a paroxysm, but the activity of the toxin is manifest or in abeyance according to the condition of the temperature.

Later observations indicate that the reaction may not be so simple, and that the condition of the serum is not in all cases the same.

A. and C. Hymans van den Bergh found that no lysis followed the

Donath-Landsteiner sequence of cooling and then heating in three cases. They showed that the cooling of blood containing the normal amount of Co_2 did not lead to lysis on subsequent rise of temperature, but that if blood was kept for two hours in contact with CO_2 and slightly cooled, a marked hæmolysis occurred when the temperature rose. They consider that the hæmolysin is composed of two substances, one absorbed by the red corpuscles, the other retained by the serum. Hæmolysis occurs when both act on the blood corpuscles. The temperature must be over 0° C. and under 37° C.

Mayer and Emmerich made the interesting observation that an attack precipitated by a cold foot-bath was ushered in by a rigor and that there was a great increase of blood-pressure, obviously due to a constriction of peripheral vessels. They also record an important observation regarding the source of complement. No free complement was found in the case of a patient after a spontaneous attack. It was found that complement could be produced locally by ligaturing one finger and immersing it in ice-water. No complement was yielded by the other fingers.

Another view of the condition is that there is no hæmoglobinæmia, and that the hæmolysis is effected in the kidney and the dissolved hæmoglobin is directly excreted. A recent exponent of this view is Scheidemantel,[1] who failed to obtain hæmolysis by the Donath-Landsteiner procedure and could never find hæmoglobinæmia. Achard and Feuillie[2] afford experimental support to this view. By the injection of muscle extracts they obtained hæmoglobinuria without hæmoglobinæmia. There was a considerable number of white cells in the urine. There is general agreement that the white cells play no active part in the production of the condition, but Meyer and Emmerich have found that the serum of "hæmoglobinurikers" has an opsonic effect in increasing the number of healthy red corpuscles taken up by large lymphocytes.

Symptoms.—The attacks may be preceded by rigors and pyrexia; in other cases the hæmoglobinuria comes on without warning after a chill or after exertion. The temperature in these cases may be subnormal. An attack can often be determined by a cold foot-bath or general immersion. Vomiting and diarrhœa may be initial symptoms. The hæmoglobinuria may last for two days but very frequently only

[1] *Münch. med. Wochenschr.*, 1909.
[2] *Soc. de Biologie*, 1909.

lasts for a few hours. In some cases there may be a succession of paroxysms in the course of a day, the urine being clear between times. Jaundice and pain in the back sometimes occur. The urine may be merely smoky in colour or may be almost black; it gives the usual tests and spectrum of oxyhæmoglobin. Total nitrogen is diminished. Phosphorus and normal urinary pigments are decreased. In from ten to twelve hours after an attack urobilinuria is usually found. "Albuminuria" often precedes an attack, and is occasionally to be found after the hæmoglobin has disappeared. This may be explained by so slight a degree of hæmolysis that the spleen and liver are able to deal with the pigment and only the globulin is excreted. There is often a deposit of hyaline or granular (pigment) casts and half-laked blood corpuscles. A few white cells are often present. No abnormal deposit is to be found in some cases.

The Blood Changes.—The paroxysms may bring about a drop in the red cell count of over one million. During the attack the colour index is high owing to the hæmoglobinæmia. There is a polymorph leucocytosis. The day after the attack there is sometimes an increase in the number of eosinophils. During the intervals there is usually a leucopenia, and the percentage of small lymphocytes may be as high as thirty-five. In severe cases grave secondary anæmia may result.

Prognosis.—Attacks are likely to recur, but the disease is not usually attended with danger to life, though we have known fatal cases.

Treatment.—Rest and warmth are essential. If a patient in spite of precautions takes repeated attacks, he should be recommended to live for some time in a warm climate. Arsenic has been recommended, and where there is a syphilitic history antisyphilitic remedies may be tried. Any drugs having a hæmolytic action, such as chlorate of potash and quinine, should be avoided, as we have seen them cause attacks in the subjects of this condition. During an attack warmth and hot drinks are indicated. Amyl nitrate has been said to cut short the attacks.

CHAPTER XXVII

BLOOD DISEASES IN INFANCY AND CHILDHOOD

For some considerable time after birth the marrow in the shafts of the long bones remains red; there is therefore comparatively little power of compensation or restoration without, at least, considerable disturbance of those blood-cells which are concerned in the reproduction of their species. It therefore follows that hæmorrhage is ill borne in children, and that any demand for an increase of blood is met by a response which involves the output of nucleated red cells into the circulation. These are in the first place normoblasts, but megaloblasts are not uncommonly found, and in rarer conditions nucleated red cells with little or no ripe hæmoglobin.

The same serious significance is therefore not to be attached to these appearances as to the corresponding blood-picture in the case of adults.

The white cells are more responsive to stimuli than in adults. A much larger leucocytosis is to be expected in the case of infections, etc., than would be likely to occur in the corresponding conditions in adults. Due regard must be paid to the leucocyte formula in health. The normal lymphocyte percentage is high in children, and this tends to be exaggerated in disease (Chap. X.).

Pernicious Anæmia and Leucocythæmia

Pernicious anæmia occurs in infancy and childhood with very great rarity (see p. 114).

Myelocythæmia (granular-cell leukæmia) is also very rare.[1]

[1] *Cases of Myelocythæmia in Infancy.*—1-6. Hutchison, *Lancet*, 1904 (could find only five authentic cases, and adds a sixth). 7. Ginsburg, *Inaug. Diss.*, Zurich, 1905. 8. Zyberlast, *Thèse de Genève*, 1906-7. 9. Falconer, *Lancet*, 1906. 10. Ziegler and Jockmann, *Deutsch. med. Wochenschr.*, 1907. 11. Benjamin, *Münch. Gesellsch. f. Kinderheilk.*, 1908. 12. Abt, *Arch. Pediatrics*, 1908. 13. Leschen and Cleland, *Austral. Med. Congress, Melbourne*, 1908 (congenital case). 14. Babonneix and Tixier, *Archiv de méd. des enfants*, 1909. 15. Dallas, *ibid.*, 1910. 16. Karsner, *Pennsylvania Med. Bulletin*, 1910. 17. Whipman, *Proc. Royal Soc. of Med.* (section, Children's Diseases), 1911. 18-20. Sternberg, *Wien. klin. Wochenschr.*, 1911 (three cases in

Lymphatic leukæmia is comparatively common. All of these diseases have the same features as in adults, but symptoms tend to be more acute.

Secondary Anæmia

Secondary anæmia is common in children as the result of deficiency in the iron or protein content of the food, rickets, diarrhœa, chronic gastro-intestinal catarrh, and acute or chronic affections. There is a diminution in the number of red corpuscles and a proportionately greater diminution in the percentage of hæmoglobin. Poikilocytosis is present, but is generally not so marked a feature as anisocytosis. Normoblasts appear in the peripheral circulation, and some of these show abnormalities of type. In the severer cases there are megaloblasts. There is polychromasia and punctate basophilia. Leucocytosis is the rule. In the more moderate instances the polymorphs are specially increased; in the more severe cases there is also an increase of lymphocytes. The spleen is very apt to be enlarged in any case in which the anæmia is severe.

Splenic Anæmia of Infants

Much confusion has arisen in connection with this condition, in part due to the high-sounding title, anæmia pseudoleukæmica infantum, applied to it by von Jaksch. It is open to question whether the condition is anything more than a severe type of secondary anæmia occurring in children, but since the splenic enlargement is a constant feature in splenic anæmia of infants, and is not a necessary feature in secondary anæmia, it may be conceded that the name is at least a useful one to distinguish a definite clinical condition.

Etiology.—The affection is found in children between the ages of six months and two years. There is a record of one case at the age of three and a half years. According to Hutchison, Jews and twin children have a special liability. The most commonly associated condition is rickets, but the disease affects only a small proportion of rickety children. Syphilis is another common antecedent.

association with acute febrile diseases). 21. Goodall, *Edinburgh Med. Journ.*, 1912. 22. Pollmann, *Münch. med. Wochenschr.*, 1898 (records a case which he regards as congenital). Cassel, *Berl. klin. Wochenschr.*, 1898, and Rivière, *Trans. Royal Med. and Chirurg. Soc.*, 1903, give references to cases which Hutchison regarded as non-authentic.

Pathology.—The spleen is enlarged, there is some overgrowth of fibrous tissue, and the Malpighian bodies are indistinct. There is chronic venous congestion, and excess of leucocytes and nucleated red cells in the sinuses. The bone-marrow is red and unusually active. A fair amount of megaloblastic proliferation may be made out. The anæmia is due to a toxin acting on the blood and bone-marrow, and the spleen enlarges to deal with the effete red cells and the excess of leucocytes.

Symptoms.—Onset is gradual. Attention is first attracted to the condition either by general ill-health, pallor, or signs of some concomitant such as rickets. The children are usually apathetic and listless. The temperature may be irregular. There is always some wasting, and there may be great emaciation. Vomiting and diarrhœa sometimes occur. There may be hæmic cardiac murmurs, and a venous bruit can be heard in the neck. The abdomen is prominent. Sometimes there is a little ascites. The spleen is greatly enlarged and may extend across to the middle line. The liver is enlarged, and in some instances its lower border is as low as the umbilicus. Lymphatic glands are not enlarged. There is marked pallor. Sometimes the skin has a peculiar waxy appearance and may be pale yellow in colour. Fowler[1] has noted a slight petechial eruption over the abdomen in fatal cases.

Blood Changes.—In an extreme case the red cells may be reduced to a million and a half per cubic millimetre. Hæmoglobin is reduced and the colour index is always low. There is great variation in the size of the cells, and this is a more striking feature than poikilocytosis. Polychromasia is a marked feature. The number of nucleated cells may be remarkable; over 2000 per c.mm. has been noted. Megaloblasts may be very numerous. Even more primitive forms and red cells with mitotic figures and cells with fragmented nuclei are not uncommon. The number of nucleated red cells has no relation to the severity of the disease.

Leucocytes.—In the great majority of cases the count is greatly increased and may reach 60,000 per c.mm. A striking feature is the large number of "transitional" cells. Fowler's differential counts were as follows:—

Lymphocytes, 34 to 76; average, 50 per cent.

[1] *International Clinics*, 1901.

Transitional cells, 1 to 24; average, 12 per cent.

Polymorphs, 20 to 43; average, 36 per cent.

Eosinophils, 0 to 7; average, 1½ per cent.

Myelocytes may be found in almost every case in which there is a leucocytosis.

Diagnosis.—In the majority of cases there is no special difficulty. The age, the enlarged spleen, the anæmia, with numerous nucleated red cells and leucocytosis, are the diagnostic features.

Prognosis.—The majority of cases do well. Death sometimes takes place from asthenia or from an intercurrent affection. The splenic tumour may disappear in from six months to a year, and the anæmia is often recovered from sooner. Unfavourable signs are marked signs of rickets or other complication; a marked diminution of red cells, and of their colour index; a high leucocyte count, especially associated with a high percentage of transitional cells; numerous myelocytes; petechial hæmorrhages. No prognostic significance can be attached to the size of the spleen, to the number of erythroblasts, the percentage of lymphocytes, or the presence of a few myelocytes. Cases which begin to show improvement generally go on to complete recovery. Cowan has reported two cases in which there seemed to be a transition from this condition to Banti's disease.

Treatment.—The chief indication is the treatment of the concomitant or causal condition. Arsenic seems to be of definite service, and iron is not of much use. X-rays are of no service, and seem even to be dangerous. In two cases reported to us their use seemed to hasten a fatal issue.

In the present state of knowledge splenectomy cannot be recommended.

CHAPTER XXVIII

CONGENITAL FAMILY CHOLÆMIA (ACHOLURIC JAUNDICE)

A CONGENITAL disease characterised by icterus, anæmia, and enlargement of the spleen.

Etiology.—In the majority of cases the disease is a hereditary or family affection, but there are exceptions. The following types occur:—

1. Hereditary and familial. Cases have been reported extending over four generations and affecting several members of a family in each generation. Males and females are affected equally, but in some of the genealogies only one or other sex has been affected throughout. No instance of an unaffected member of a family transmitting the disease has been reported.

2. Family cases without history of hereditary transmission.

3. Isolated cases occuring at birth or in infancy.

4. Cases in which symptoms do not appear till early adolescence or adult life.[1]

Pathology.—Only a few post-mortem reports appear to have been published. The liver shows no special change. Fatty degeneration has been noted in one case. There is no cholangitis unless gall-stones have been present. The spleen was enlarged in all recorded cases, and there was perisplenitis. Some fibrosis has been noted, but the chief change is simple engorgement and pigmentation mainly in the endothelial cells. The kidneys may show pigmentation and slight interstitial change. The bone-marrow in one case was red throughout the whole length of the femur and in a condition of great activity. The disease is probably due to a diminished resistance of the red cells, which may be accounted for by the presence in the plasma of a

[1] There is reason to suppose that a distinction should be drawn between the "congenital" or "family" cases and the acquired form. Aschenheim (*Folia Hæmatologica*, xi. Teil, 1911, 1) discusses a case in point by the name of "Toxic-hæmolytic Icterus with Splenomegaly."

hæmolytic toxin of unknown origin, but it is possible that in some cases at least the function of the spleen may be so exaggerated that it breaks up corpuscles of normal fragility. The jaundice is due to over-production of bile pigments.

Symptoms.—A feature of the disease is its comparatively slight effect on the general health. Advice may be sought on account of the coloration rather than because of any special disability. Jaundice is an important symptom, but the diagnosis might be possible in its absence in the event of a second case in one family. It is very rarely altogether absent, but its intensity varies very greatly from time to time. It seldom reaches the degree seen in cases of obstructive jaundice, but the conjunctivæ are usually definitely coloured and bile pigment can usually be demonstrated in the blood serum. Patients may complain of impaired general health during the attacks of increased icterus. The stools are well coloured, and there is no less of fat or alteration in the proportions of fat, fatty acids, and soaps. In the case recorded by Mackintosh, Falconer, and Anderson the stools were always more deeply coloured with bile on the occasions on which their patient became more deeply jaundiced. The liver is either not at all or only very slightly enlarged. The spleen is enlarged as an early symptom in the great majority of cases. The exceptions are rare. The organ may extend to the level of the umbilicus or even lower, and in time becomes very hard.

The majority of the cases are acholuric, but in a few bile pigment has been found in the urine at long intervals. Urobilin is generally present. During the periods of increased jaundice there is generally a heavy deposit of urates. Attacks of pyrexia may occur.

Epistaxis is a symptom of fair frequency. Retinal hæmorrhages and purpuric spots have been recorded in one instance. Paroxysmal hæmoglobinuria was present as a complication in one case.

The Blood Changes.—There is usually a definite anæmia. Red cell counts of about two millions are common; instances have occurred of counts below one million. Poikilocytosis is present, but irregularity in size is a more marked feature. The average size of the red corpuscles is much diminished. This microcytosis may be looked upon as one of the essential features of the disease. Polychromasia and punctate basophilia are fairly common, and the proportion of corpuscles showing reticular substance after vital staining may reach 8 per cent.

instead of the usual one or two. Nucleated red cells are to be found in the more severe stages of the disease. These are mainly normoblasts, but a few megaloblasts may be found.

In one recorded case there were attacks of cyanosis with increase of the jaundice, and during these attacks the number of red cells rose from 6,000,000 to 7,600,000. The hæmoglobin is diminished to a greater degree than the red cells, so that the colour index is low.

The leucocyte count does not show any special abnormality. The recorded differential counts vary considerably, but that is just what might be expected in a condition mainly affecting children. Myelocytes in small numbers are generally found. Bile is always present in the blood-serum, but urobilin is not found, and hæmoglobin has been found in only two cases, and one of these was complicated by paroxysmal hæmoglobinuria. The resistance of the blood to hæmolytic agents is diminished (see page 46). Whereas normal human red corpuscles do not undergo hæmolysis in salt solutions stronger than 0·4 per cent., the blood corpuscles in this disease may be dissolved in 0·7 or 0·6 per cent. salt solution.

Diagnosis.—The conditions which may resemble this disease are as follows :—

1. *Congenital Anæmia with Jaundice from Obliteration or Narrowing of the Bile-Ducts.*—In these cases the liver is enlarged, the urine is definitely bile-stained. There are often hæmorrhages. The blood tends to be megalocytic instead of microcytic, and the resistance to hypotonic salt solution and other hæmolytic agents is increased rather than diminished.

2. *Hypertrophic Cirrhosis of the Liver.*—This affection is sometimes met with as a family disease. The liver is enlarged, there is jaundice with bile pigment in the urine, the children are deficient physically and often mentally. The blood changes are those of somewhat mild secondary anæmia.

3. *Congenital Syphilis.*—The presence of signs of syphilis apart from those common to the two conditions and the Wassermann or luetin reaction would distinguish this disease.

4. *Pernicious Anæmia.*—Cases of pernicious anæmia in infants are excessively rare. It may be difficult to distinguish it from cases of acholuric jaundice developing at or after puberty. Cases of what seem to us clear examples of pernicious anæmia have been recorded as acholuric jaundice. The chief diagnostic point must be the examination

of the blood. The megaloblastic and megalocytic anæmia with high colour index, and the leucopenia with the relative lymphocytosis of pernicious anæmia, contrast strongly with the typical changes in acholuric jaundice. It should not be forgotten that a slight degree of jaundice is not uncommon in acute cases of pernicious anæmia.

5. *Splenic Anæmia.*—Both the ordinary type and the Gaucher type may be family diseases. Jaundice is absent in the ordinary form until the stage of Banti's disease is reached, but has been found in cases of the Gaucher type. The blood changes are comparatively slight in the early stages, and differ from those of acholuric jaundice throughout (Chap. XVIII.).

Prognosis.—The disease is very rarely fatal and has very little tendency to shorten life. Several female cases have been mothers of large families. The cases developing in later life are much more serious than the cases with symptoms developed at birth or in infancy. The older cases as a rule show more anæmia and less jaundice than the infantile cases.

Treatment.—Treatment is seldom called for, and in many instances is only required to meet special symptoms. Arsenic appears to be of no use. When symptoms are distressing or causing much disability the question of splenectomy may be considered.

A small number of cases of apparently complete recovery after this procedure are now on record, but the operation is not without risk. Operations for complicating gall-stones appear to have been successfully performed in two cases. One case of cholecystectomy was fatal.

Literature

An admirable account of the disease and full references are given by Mackintosh, Falconer, and Anderson, *Edinburgh Med. Journ.*, March 1911.

Congenital Anæmia with Obstructive Jaundice

A group of cases has been described in which anæmia, jaundice, and varying degrees of biliary obstruction have been the chief features. Only a few cases have been studied by modern hæmatological methods. The disease may affect several members of one family in which the parents have been healthy. Single cases in a family have occurred. The liver

shows evidence of biliary obstruction, either through congenital obstruction or obliterative cholangitis.

In Buchan and Comrie's cases there were erythroblastic areas in the liver; the bone-marrow was very active. At the same time there was evidence of destruction of blood corpuscles by circulating phagocytes and by endothelial cells in the lymph glands and spleen. The iron reaction was found in the spleen. The disease is probably due in part to the hæmolytic action of the bile and in part to the retention of toxins which are normally taken up and excreted by the liver.

Symptoms.—The symptoms are jaundice at birth or developing very shortly afterwards. The urine is bile-stained, the fæces are acholic. The liver and spleen are enlarged. Hæmorrhages are common. There is profound anæmia. Red cells number roughly from $1\frac{1}{2}$ to $2\frac{1}{2}$ millions. The colour index tends to be high. The average size of the corpuscles is increased. Poikilocytes are not specially numerous. Polychromasia is very marked, and punctate basophilia is generally present. Nucleated red cells are very common, and megaloblasts often preponderate. In addition to megaloblasts there are numerous cells of a more primitive type. Cells with mitotic figures and pyknotic nuclei may be found. There is very marked leucocytosis. The percentages of the different varieties are not greatly different from the infant formula in health. Myelocytes are present in fair numbers. Eosinophils are in normal proportions; a few show immature (basophil) granules. Some of the large lymphocytes show evidence of phagocytosis of red cells. The blood-plates are diminished. The red cells show a high degree of resistance to hæmolytic agents.

Prognosis.—The great majority of cases die within ten months of birth. A few cases, however, have recovered completely.

Literature

Buchan and Comrie, *Journ. of Path. and Bact.*, xiii. 1909.

CHAPTER XXIX

LYMPHATISM—STATUS LYMPHATICUS—STATUS THYMICUS

A DISEASE associated with an enlarged thymus and hyperplasia of lymphoid tissue, characterised by a tendency to sudden death.

Etiology.—The condition is found in children and more rarely in young adults. The actual cause of the condition is altogether obscure. It has been suggested that it is due to malnutrition in early childhood. Some cases have occurred in epileptics, and rickets is not uncommonly associated with it.

Pathology.—The principal morbid change found is an enlargement of the thymus. The change chiefly consists in a hyperplasia of the glandular tissue. The Hassall's corpuscles may have the usual concentric structure or may exhibit the stage before the formation of the concentric bodies, viz. healthy and broken-down epithelial cells invaded by polymorphonuclear leucocytes and lymphocytes. The follicles at the base of the tongue, the tonsils, and the Peyer's patches and solitary follicles may show enormous enlargement. The Malpighian bodies of the spleen and varying groups of lymphatic glands are also enlarged. The heart is often dilated, its muscle is flabby, and in some cases a narrowing of the aorta has been described. The bone-marrow is often red in the shafts of the long bones, even in adults. The thyroid has been enlarged in a fair proportion of cases.

The sudden death which takes place in so many of the cases is due in some instances to compression of the trachea by the enlarged thymus. This is especially likely to occur in young infants, but ordinarily the enlargement of the thymus is only a part of the lymphoid hyperplasia, and the condition is probably to be regarded as one of chronic toxæmia.

Buzzard calls attention to the similarity between some of the cases and cases of myasthenia gravis. In the latter condition there are collec-

tions of lymphocytes in the organs, tissues, and muscles. The thymus is enlarged in over 50 per cent. of cases, and death often occurs suddenly from failure of the respiration or heart. Again, it has been sought to establish a connection between lymphatism and exophthalmic goitre, in which the thymus is often enlarged. Mair reports a case associated with Zenker's degeneration of the muscles.

Symptoms.—The recognition of the condition during life is difficult, and the diagnosis is very seldom made. There is pallor. The temperature is often subnormal. There may be evidence of an enlarged thymus in the existence of an area of percussion dulness in the region of the manubrium sterni, but this dulness is often not well marked. Sometimes the enlarged thymus tends to push down the heart so that the upper border of the superficial cardiac dulness is lowered. There is hypertrophy of the tonsils and the lymphoid tissue about the mouth. Sundry groups of lymphatic glands, especially those about the neck, may be enlarged. The tongue is large as a whole and the papillæ are prominent. There is sometimes a symmetrical enlargement of the thyroid gland. The heart sounds are muffled and faint. The pulse is slow and the blood-pressure is diminished.

The outstanding feature of the condition is the remarkable tendency to sudden death from apparently trivial or undiscoverable causes. The occurrence of sudden death (*thymus tod*) is generally the first intimation of the presence of the condition. In some cases there has been stridor for a few weeks. In other instances there have been increasing attacks of dyspnœa, but usually there is simply cessation of respiration or of the heart without warning. The antecedent circumstances have been very diverse. Some cases have been found dead in bed. Trivial occurrences such as a slight burn or a hypodermic injection of diphtheria antitoxin or of cocaine for local anæsthesia have been followed by death. In other cases the fatal result has followed a fright or emotional condition or bathing. Particular attention has been attached to those cases following the administration of a general anæsthetic.

Thursfield has reported a case in which death occurred in his presence without apparent cause.

"A boy, aged thirteen months, was admitted to the wards with rickets and tetany. The last was very slight; a fit was said to have occurred on the previous day. While I was standing at the side of the cot the child suddenly sat up, its eyes became fixed, it ceased to breathe, became very slightly blue, then quite white, and fell back dead. The

whole series of events occupied less than thirty seconds. There was certainly no question of asphyxia; it appeared rather as if both circulatory and respiratory centres struck work simultaneously."

Bellamy Gardner gives an admirable account of an anæsthetic case. Patient was a boy, aged thirteen. The anæsthetic was chloroform one part, and ether two parts, by volume. The operation was for the enucleation of deep-seated tonsils and very large adenoids. Anæsthesia was induced uneventfully.

"At this third sweep of the curette the patient made a very slight retching movement, and a little bluish blood appeared in the pharynx; his head and body were rotated to the right side for drainage, and a teaspoonful of bilious fluid was ejected from the right corner of the mouth and he stopped breathing. The throat was sponged. I squeezed his chest; air escaped and entered audibly. I looked into the pharynx and felt behind the tongue; there was no blood or other obstruction there. Suddenly a deep navy blue colouration appeared on the forehead and temples, slanting away towards the ears, with a definite border along the zygomatic arch. The lips, ears, and face were at the same time almost normal in colour. The corneal reflex now disappeared, and the pupil, which had been about $2\frac{1}{2}$ mm. in diameter, enlarged to 4 or $4\frac{1}{2}$ mm. From the moment of the respiratory paralysis not one single natural muscular or respiratory movement ever took place."

The Blood.—There is anæmia of a chlorotic type. The leucocyte count may be slightly increased. There is a moderate lymphocytosis, absolute or relative.

Treatment.—Unfortunately most cases are beyond the reach of treatment before the diagnosis is made. Should a case be recognised during life it is obvious that special care will be demanded in the avoidance of disturbances which might lead to a fatal termination. Since arsenic does good in many forms of lymphoid hyperplasia, it would be worth a trial in this disease. Rachford[1] has treated two cases successfully with X-rays. While it would be unwise to exaggerate the danger of anæsthesia, owing to the possibility of lymphatism, it would be folly to minimise it. In cases of possible operation, where there is lymphoid hypertrophy, it would be well to examine closely for indications of the

[1] *Amer. Journ. of Med. Sci.*, October 1910.

disease, since the induction of anæsthesia and the operation *per se* are fraught with special risks when it is present.

Literature

Paltauf, *Wien. klin. Wochenschr.*, ii. 1889, 877. Gardner, Buzzard, Humphry, and others, *Proc. Roy. Soc. of Med.* (Sect. Anæsthetics), 1909-10. Thursfield, *St. Bart.'s Hosp. Reports*, 1903, 129. Buxton, *Lancet*, 6th August 1910. Mair, *Med. Chronicle*, January 1911.

PART IV

THE BLOOD IN SPECIAL DISEASES

CHAPTER XXX

INFECTIOUS DISEASES

Introduction.—In febrile conditions blood-counts may be affected by vasomotor disturbances, but only to a very slight extent. During the course of the fever there may be concentration of the blood due to contraction of vessels and to loss of fluid. After a fever there is often dilatation of vessels and a corresponding drop in the blood-counts. In most fevers there is a considerable leucocytosis. (The exceptions are stated on p. 76.) The extent of the leucocytosis depends on the nature of the infection, its severity, and the powers of resistance of the organism. An infection may be so slight that no stimulus is given to the bone-marrow, and no increased number of leucocytes is sent out, or so severe that the bone-marrow is poisoned before it can react. Between these extremes there may be a varying degree of stimulation and a varying amount of reaction. Leucocytosis is not dependent on the rise of temperature. The degree of fever and the extent of the leucocytosis seldom correspond, and show variations independent of each other. In most of the common fevers the blood-plates are diminished in number.

Scarlet Fever.—The red corpuscles are affected only in severe cases. In these there may be a drop of half a million. The white cells show very definite changes. These have been very fully studied by Bowie,[1] who finds that practically all cases show leucocytosis, which begins in the incubation period very shortly after infection, reaches its maximum at or shortly after the height of severity of the disease, and then gradually sinks to normal. In simple uncomplicated cases the maximum is reached during the first week, and the normal generally

[1] Bowie, *Journ. of Path. and Bact.*, 1902, 82.

some time during the first three weeks. The more severe the case the higher and more persistent is the leucocytosis. A favourable case in any one variety of the disease (simple, anginose, etc.) has a higher leucocytosis than an unfavourable one of the same variety. Bowie's highest count in simple cases was 35,000, in anginose cases 43,000. The polymorphs are increased relatively and absolutely, and may constitute 90 per cent. of the total.

Eosinophils are diminished at the onset of the fever. They increase rapidly in simple favourable cases till the height of the disease is past. They may number 11 per cent. on the third day. Eosinophilia may persist after the total count has reached normal. The more severe the case the longer are the eosinophils subnormal before they rise again; in fatal cases they never rise, and generally disappear altogether from the circulation. The behaviour of the eosinophils may be of diagnostic value in mild cases. The increase of these cells early in the disease may help to distinguish it from cases of tonsillitis and septic conditions.

Klotz [1] has described diminished staining affinities of the eosinophils in malignant cases, and in these the leucocytes show a well-marked glycogen reaction. In complications the leucocytes go through a cycle of events similar in all respects to that of the primary fever.

According to Tschistowitsch [2] the blood-plates may be normal or diminished on the first day of the disease, but thereafter show an abrupt increase. Complications associated with fever cause a temporary diminution.

Inclusion Bodies.[3]—In 1911 Döhle described what he called "inclusion bodies" in the leucocytes in cases of scarlet fever. These bodies are easily demonstrated in films by any of the ordinary basic stains (carbol-methylene blue, carbol-thionin, etc.) after fixation. They are found in the protoplasm of polymorphonuclear cells only, and are round, oval, or slightly elongated bodies which closely resemble micrococci. They are probably products of degeneration in the cytoplasm. They are present in at least 90 per cent. of cases of scarlet fever during the first four days. They are sometimes absent in severe fatal cases. After the fourth day they diminish in number, but generally persist for at least a week. The bodies are also found, though in smaller numbers, in measles, rötheln, diphtheria, tonsillitis, typhus, etc., and

[1] Klotz, *Journ. of Infect. Diseases*, 1904, 404.

[2] *Folia Hæmatologica*, iv. 295.

[3] See Granger and Pole, *Brit. Journ. of Children's Diseases*, January 1913, and M'Ewan, *Journ. of Path. and Bact.*, 1914, 456.

in most diseases caused by pyogenic organisms. They are absent in cases of serum rashes and other toxic eruptions, so that the fact of their presence or absence may have slight diagnostic value in some cases.

Measles.—Most observations indicate that there may be a slight or more rarely a marked leucocyte increase, with increased percentage of polymorphs, during the incubation stage. During invasion the number diminishes, and during and after the eruption there is leucopenia associated with a high percentage of large lymphocytes. Eosinophils are diminished, and do not return to normal till desquamation has begun. All complications produce leucocytosis. The diagnostic value of the leucopenia is very considerable.

Rotheln.—The leucocyte changes are similar in character to those of measles, but are less marked and much less constant. Red corpuscles and blood-plates are not affected.

Mumps.—Feiling[1] found a slight increase of white cells with lymphocytosis, which was present on the first day, and persisted for at least a fortnight. Orchitis did not alter the blood-picture, but other observers have found that orchitis generally produces a slight polymorph leucocytosis.

Whooping-Cough.—Churchill[2] found lymphocytosis in 93 per cent. of 42 cases in the catarrhal stage. Crombie[3] studied 112 cases, and found that lymphocytosis, either absolute or relative, was constant. His average count in the catarrhal stage was 20,237 white cells per c.mm., with 66 per cent. of lymphocytes. In whooping-cough the divergence from the normal blood-picture is so great that it is seldom necessary to consider the age of the child. A high leucocytosis at the outset points to a severe and prolonged attack. In the later stages the leucocyte count varies directly with the number and severity of the paroxysms.

Cases complicated with pneumonia may show very high leucocyte counts. Crombie reports the case of a child of twenty months with 233,000 per c.mm., of which 58 per cent. were lymphocytes. Similar

[1] *Lancet*, 12th July 1913, 71.
[2] *Journ. Amer. Med. Assoc.*, 1906, 1506.
[3] *Edin. Med. Journ.*, 1908, 3.

cases have been reported by other authors. The lymphocyte increase has been ascribed to irritation of the bronchial lymph-glands, but these could not possibly supply so large a quantity, and as the polymorphs are so greatly increased also in total number, though not in proportion, there is every reason to believe that both increases are derived from the bone-marrow, and are chemiotactic in origin.

Influenza. — In a prolonged or severe case there may be slight anæmia. In uncomplicated cases there is no increase of white cells, and even in cases with slight broncho-pneumonia the rise may be absent or ill-marked. This normal count is often of great value in excluding septic processes when fever is long continued, but gives no help in the diagnosis from tubercle or typhoid.

Diphtheria.—Slight anæmia may occur, less marked if antitoxin be given early. Sometimes the blood becomes concentrated at the height of the disease, and the count is higher than normal. The white cells are usually increased in number; a common figure is 20,000. In very mild and very severe cases leucocytosis is commonly absent. The cells causing the increased counts are the polymorphs. The leucocytosis is practically unaffected by serum treatment, and it may persist for a short time after the disappearance of the membrane. The glycogen reaction is not present unless there be much local inflammation. Blood-plates show a marked and persistent reduction.

Typhoid.—The red corpuscles during the first two weeks show very little, if any, change. In the third week a diminution, which may become considerable, begins. Counts falling below 2,000,000 have been recorded. As is usual in secondary anæmia, the hæmoglobin loss is rather greater than that of the erythrocytes. There may be a transient slight initial leucocytosis, but in the absence of complications there is usually none. Almost at the outset an increase of lymphocytes, especially of the large forms, begins at the expense of the polymorphs. This change becomes progressively more marked, and in the later stages there is an actual leucopenia, due to a diminution of polymorphs. This leucopenia may occur early. We have repeatedly seen counts of 4000 in the first week, but it is more usual to have a practically normal count at that stage. Perforation is usually associated with leucocytosis, unless the patient be already profoundly poisoned. Eosinophils are diminished, and their disappearance before the third week is

of unfavourable omen. Late complications with mixed infection usually show leucocytosis, but as a general rule the polymorph proportion in these cases is not so high as it would be in the absence of typhoid. This holds for such complications as periostitis, terminal pneumonia, cholecystitis, pleurisy, and empyema. The absence of leucocytosis and the high percentage of lymphocytes are of very great value in diagnosis, and in many cases the blood examination will clear up a diagnosis of typhoid before the Widal reaction is available. The glycogen reaction is never intense, and does not appear before the end of the second week.

Eberth's bacillus is found in the blood, and can be cultivated in the great majority of cases in the second and third weeks.

Cummins recommends a solution of 0·5 per cent. taurocholate of soda in water as a useful medium for early diagnosis. Only 1·5 c.c. of blood need be added to 5 c.c. of the bile water.

The conditions which are most often mistaken for typhoid can in the majority of instances be diagnosed from it by a blood examination, if thorough physical examination leaves doubt in the mind of the attendant. Judging from the statistics of fever hospitals, pneumonia is the most frequent error. Here the leucocytosis which occurs in nine cases out of ten, at least, with the high polymorph percentage and marked glycogen reaction, should prevent mistake. The very slight cases with moderate or absent leucocytosis are not likely to cause error, as in them there is hardly ever sufficient distension of the abdomen or sufficient disturbance of digestion to induce the thought of typhoid. The severe cases with leucopenia are most likely to be notified as typhoid, for they may show marked abdominal distension, and in the differential count the polymorph percentage *may* be as low as 60, but the glycogen reaction is always so intense that nothing but a severe peritonitis in typhoid could equal it. The pneumonia which occurs occasionally early in typhoid does not in our experience greatly raise the leucocyte count, the polymorph percentage is not high, and the glycogen reaction, if present at all, is always slight.

In those cases of influenza which show protracted fever and which sometimes resemble typhoid, the blood will not help, and Widal's reaction, the diazo test, etc., must decide the difficulty. The same holds with regard to acute miliary tuberculosis, in which case a persistently negative Widal, and the fact that the bacillus typhosus cannot be isolated from the blood, may sometimes be the only means of distinguishing the two conditions.

Tuberculous meningitis gives a leucocytosis with increased poly-

morph percentage so constantly that the great majority of doubtful cases may be distinguished in this way. We have, however, seen cases with counts of 7000 and 8000 at the beginning of illness, but these developed higher counts when followed up. There are certain cases of typhoid, moreover, in which there is persistent leucocytosis throughout, with no discoverable complications, but these are very rare.

Acute enteritis always shows a rather high leucocytosis, 20,000 to 25,000; and appendicitis, of the type likely to be mistaken for typhoid, also has usually both a leucocytosis and a definite glycogen reaction.

Typhus.—Recent observations have been made by Love,[1] Slatinéano and Galesesco,[2] and Lucksch.[3] The red cells may be increased during the fever, but anæmia with poikilocytosis soon becomes marked. Leucocytosis is the rule; it may appear before or with the eruption. The leucocytosis usually increases just before the crisis, and falls on the day following, but the count does not reach normal till convalescence is established. The leucocytosis is mainly polymorphonuclear, but lymphocytes are also increased, and in the later stages may reach percentages of 45 or 50. Eosinophils are diminished, and may be absent in fatal cases. Blood-plates are increased.

Smallpox.—When the temperature falls a considerable diminution of red cells is found. Nucleated red cells may be present in small numbers, especially in hæmorrhagic cases. There is leucocytosis from the beginning, but it is greatest during the vesicular stage. The increase chiefly affects the lymphocytes, which may amount to 60 per cent. Myelocytes of all kinds may occur, and pro-myelocytes are not uncommon. The blood-picture is the same in all varieties of the disease, and is not modified by complications. The changes persist well into the convalescent stage.

Varicella.—There may be a slight polymorph leucocytosis, but the total count per cubic millimetre is frequently unaffected. A relative lymphocytosis has been noted in the later stages, but is not constant.

Vaccination.—There may be a moderate polymorph leucocytosis, beginning on the third or fourth day and lasting till the seventh

[1] *Journ. of Path. and Bact.*, x. 1905.
[2] *Société de Biologie*, lxi. 1906, 85.
[3] *Folia Hæmatologica*, iv. 1907, 520.

or eighth day. This is followed by leucopenia, and occasionally by a slight lymphocytosis.

Epidemic Cerebro-Spinal Meningitis.—Leucocytosis is the rule. Fowler found counts ranging from 14,000 to 38,000, and there was almost constantly a positive glycogen reaction.

Cholera.—Biernacki [1] found red cell counts exceeding 7,000,000 owing to the concentration of the blood. The specific gravity may be increased to 1072. Leucocytosis is an early symptom, and is greater than mere concentration of the blood would account for. The count may reach 60,000. The increase consists of polymorphs. Rogers [2] found similar changes with diminution of eosinophils. Rogers [3] has also shown that the determination of the specific gravity of the blood is of supreme importance in cholera. If the specific gravity is below 1062 the case is only a mild one; the vomiting and diarrhœa have not deprived the blood of more than one-third of its plasma, and treatment with saline infusion is not required. If the specific gravity is between 1062 and 1066, as much as one-half of the fluid may have been lost from the blood, the case is a severe one, and 80 ounces of saline solution should be administered. In severe cases as much as two-thirds of the fluid may be lost from the blood, and its specific gravity is therefore raised to from 1067 to 1076. In such cases 120 ounces of saline must be at once administered.

Dysentery.—The red cells are not affected in early cases, but in chronic cases secondary anæmia develops. In the great majority of cases there is a polymorph leucocytosis. Rogers [4] found that counts above 15,000 per c.mm. were very rare in bacillary dysentery, but that much higher figures were usually found in amœbic cases. A leucocytosis of over 20,000 occurring in dysentery is an almost certain indication of its amœbic nature, and the degree of leucocytosis is proportionate to the severity of the condition. Eosinophilia has been recorded in amœbic dysentery.

Yellow Fever.—Cabot found a polymorph leucocytosis in some cases,

[1] Biernacki, *Deutsch. med. Wochenschr.*, 1895, 795.
[2] Rogers, *Lancet*, 1902, 659.
[3] Rogers, *Cholera and its Treatment*, London, 1911.
[4] Rogers, *Dysenteries*, Oxford Medical Publications, 1913.

not in others. Eosinophils were diminished. Seidelin has described protozoon-like bodies in the blood.

Dengue.—Red cells are not much altered. Leucopenia (diminution of polymorphs) seems to be constant. There may be eosinophilia late in the disease.[1]

Bubonic Plague.—According to Rogers the blood changes met with are of some practical importance, but are too inconstant to be absolutely relied on. Hæmoglobin and red cells are not usually diminished and may be increased. A slight leucocytosis is generally present in the first three days, but may be absent later, especially in favourable cases. The proportion of lymphocytes is frequently but not constantly increased. Bacilli have been found in films of the blood.

Malta Fever.—Anæmia may be developed. The leucocytes are usually unaffected or, in the long-standing cases which we see in this country, may be diminished. The micrococcus melitensis can be found in the blood, and the cocci are agglutinated by the serum of Malta fever patients.

Anthrax.—Few observations have been made. Leucocytes increase to 10,000 or even 50,000. Eosinophils disappear after the fourth day.

Tetanus.—Red corpuscles are diminished. Luna found leucocytosis of polymorphic type (20,000-38,000). In all our cases there has been leucocytosis, but the counts have not been so high. Glycogen reaction was absent. Cabot in a fatal case found persistence of eosinophils.

Glanders.—Cases with leucocytosis of 13,000 and 16,000 have been recorded.

Hydrophobia.—Polymorph leucocytosis has been found in man and animals. Leucocytosis is induced by antirabic treatment, and França has noted an increase (2·4 per cent.) of mast cells.

Beri-beri.—In an acute case Takasu[2] found a few normoblasts.

[1] See *Folia Hæmatologica*, iii. 618, and v. 477.
[2] See *Folia Hæmatologica*, i. 1904, 501, 502.

White cells were not much altered. In six cases in Chinese sailors Marshall[1] found no anæmia and no alteration of white cells.

Tuberculosis.—In a disease with such various manifestations and with such varying relationships between virulence of infection and resistance of the tissues it is not surprising to find great variations in the blood in different cases and stages of the disease. It may be stated as the rule that in uncomplicated tuberculosis there is a diminution of red cells and hæmoglobin and an increase of lymphocytes, which may be balanced by a corresponding diminution in the number of polymorphs. Glycogen reaction is absent. Tubercle bacilli can be demonstrated in the blood in some cases, but the procedure is difficult and the results uncertain. Injections of tuberculin are followed by an increased leucocyte count. There is an increase of neutrophils and frequently also of lymphocytes.

The diagnosis of cases of continued fever without very definite physical signs is often by no means simple. The chief conditions giving rise to difficulty are typhoid fever, influenza, chronic septicæmia and deep-seated abscess, lymphadenoma with enlargement of internal glands only, and tuberculosis. The existence of typhoid can be ascertained by the middle or end of the second week by means of the Widal reaction, but it may not be possible to distinguish between tuberculosis, early typhoid, and influenza by ordinary methods of blood examination. The other conditions are all associated with a leucocytosis varying in degree with the severity of infection and the resistance of the patient.

An increasing amount of importance is being attached to Arneth's method as a guide to diagnosis and prognosis (page 76).

White Robertson maintains that the Arneth blood-picture is not affected by such conditions as acute and chronic sepsis, pneumonia, influenza, typhoid, dysentery, and mucous colitis whether there be a leucocytosis or leucopenia. He gives the following figures from cases of pulmonary tuberculosis :—

Class.	I.	II.	III.	IV.	V.
Normal	5	35	41	17	2
Early case	18	36	40	6	2
„ (improved)	6	38	45	11	0
Moderate case	26	39	29	6	0
„ (improving)	10	46	36	8	0
Advanced case	31	49	17	3	0
Dying case	65	33	2	0	0

[1] *Edin. Med. Journ.*, May 1911.

1. *Acute Miliary Tuberculosis.*—The red cells are usually not much affected, but there may be a moderate degree of anæmia. There is generally a marked diminution in the number of leucocytes, and the decrease affects lymphocytes and eosinophils rather than polymorphs.

2. *Acute Pneumonic Phthisis.*—Patients are generally anæmic from the first or soon develop anæmia. The leucocyte count is usually below normal, and continues low throughout. This low count may be the first intimation to the attendant that the disease is not the true pneumonia which it often so closely resembles.

3. *Pulmonary Phthisis.*—(*a*) In early stages the blood may show little change, but anæmia of varying degree is common. It is usually slight, but may be severe enough to give rise to symptoms. These symptoms, especially in young women, may indeed lead to the real state of affairs being overlooked, and true chlorosis and tuberculosis may co-exist. In tubercular anæmia the colour index is very rarely so low as in chlorosis, and with open-air treatment we have usually found the blood return to normal in cases that were doing well, without the necessity of giving iron. The leucocytes are usually diminished in number, the polymorphs especially being affected. The eosinophils show no constant change. The glycogen reaction is absent.

(*b*) In the intermediate stages anæmia is not so constant a feature as at the outset, and changes in the number of red corpuscles and percentage of hæmoglobin are of more service as an indication of the progress of the disease. The leucocyte count varies, but leucopenia with relative lymphocytosis is the rule.

(*c*) In advanced cases there is practically always a diminution in the number of red cells and a proportionately greater reduction in the percentage of hæmoglobin. Polymorphs become increased and the total leucocyte count may be a high one in hectic cases as long as there is some power of resistance. Eosinophils are greatly diminished or absent. The glycogen reaction may be well marked. These white cell changes are the result of the septic rather than the tuberculous infection.

4. *Pleurisy—Peritonitis—Pericarditis.*—Anæmia may occur, but is not necessarily a feature of these conditions. The white cells are either unaffected or there is a lymphocytosis, relative or absolute. An important diagnostic point is the absence of any increase of polymorphs which accompanies inflammations of the serous membranes due to most other causes.

5. *Tuberculous Meningitis.*—Anæmia advances with the progress of the disease, but is seldom marked. As distinguished from other forms

of tuberculosis, an increased leucocyte count is the rule. A count of 12,000 in the first week is very commonly met with. The increase is mainly due to polymorphs. There is occasionally a slight glycogen reaction, but never so marked as in meningitis due to other organisms. There are some cases in which the leucocyte count is not raised, especially early in the case, but the polymorph percentage is usually high.

6. *Tuberculosis of Bones and Joints.*—As long as mixed infection is absent there is no change in the red cells. The white cells may show no change or there may be lymphocytosis, relative or absolute. The absence of any polymorph increase may be of diagnostic importance.

7. *Tuberculous Adenitis.*—The changes described above apply to this condition.

8. *Tuberculosis of the Alimentary and Genito-Urinary Tracts.*—As a rule the blood shows little change, and examination of the blood gives little help in diagnosis. There may be secondary anæmia according to the severity of the condition, especially if there be hæmorrhage. As regards the white cells, the absence of retention and consequent absorption of toxins tend towards a negative blood-picture, even when a mixed infection is present.

Syphilis. — There is no appreciable change in the primary stage. Diminution of red cells and, to a greater extent, of hæmoglobin is practically always a feature of the secondary stage. There is generally a definite increase in the white cells, the lymphocytes being chiefly involved. Eosinophils are not diminished. In cases with no actual leucocytosis there is a relative lymphocytosis. The administration of mercury causes an increase of red cells, hæmoglobin, and of polymorphs, an effect which may persist for a fortnight or, in some cases, even for a month. After that period the mercury loses its stimulating effect on the bone-marrow, and may even begin to cause gelatinous degeneration.

Cases of tertiary syphilis often afford very marked examples of secondary anæmia. There may be very great reduction in the number of red cells and the amount of hæmoglobin. Normoblasts and even a few megaloblasts may be present. There is usually a leucocytosis with a high percentage of lymphocytes, and a few myelocytes are frequently to be found. The spirochæta pallida can be found in the blood in secondary syphilis and in infants suffering from congenital syphilis. As a rule a fairly large amount of blood must be taken and mixed with ten times its volume of $\frac{1}{3}$ per cent. acetic acid. This is

centrifuged, and films are made from the deposit. After drying in air films should be fixed with absolute alcohol or alcohol-ether for from ten to twenty minutes, or in methyl alcohol for five minutes. Staining may be carried out by Giemsa's method (Giemsa 1 in 15 for an hour). Leishman's method also gives good results after prolonged staining. Silver methods or any of the methods for demonstrating flagella may be employed.

A more simple method of demonstration is Burri's. Some of the deposit is mixed with an equal quantity of a solution of Indian ink in distilled water, a smear is made on a slide and allowed to dry, the spirochætes stand out white on a dark background. Still another method is by means of the dark-ground illumination.

Leprosy.—The data are scanty. Anæmia is not marked until severe lesions or complications have developed. There is no increase in the number of leucocytes. There is a relative increase of cells of the lymphocyte series. The weight of evidence is that eosinophils and basophils are not increased. The bacilli have been found in the blood.

Actinomycosis.—Ewing and Cabot report cases with 20,000 and 30,000 leucocytes per c.mm.

Blastomycosis.—In a case affecting the lungs and alimentary canal we found 3,720,000 red corpuscles, 55 per cent. hæmoglobin, and 8200 leucocytes, of which 76 per cent. were polymorphs, 24 lymphocytes. No eosinophils were seen.

CHAPTER XXXI

SEPTIC AND INFLAMMATORY CONDITIONS

Introduction.—In these conditions the blood may be slightly or profoundly altered, according to the severity, extent, and duration of the process.

There is always anæmia, which may be induced very rapidly. In severe cases there are marked degenerative changes in the red cells, and normoblasts are found in the peripheral circulation.

Leucocytosis is the rule. Other things being equal, a suppurative inflammation is associated with a greater leucocyte count than a plastic process. The absorption of toxins is an important factor. An unopened abscess of small dimensions is associated with a greater leucocytosis than a drained empyema. Leucocytosis is generally absent in cystitis. A progressive inflammation may cause a greater leucocytosis than a walled-off abscess. The common pyogenic cocci usually cause greater leucocytosis than other organisms. The pyogenic infections are associated with the glycogen reaction in the leucocytes. Blood-plates are generally increased.

While the leucocytosis associated with septic and inflammatory conditions is usually accounted for by an increase of neutrophil polymorphs there appear to be certain exceptions. Thus Cabot [1] has recorded cases of wound infection, boils, and septic adenitis with high lymphocyte percentages. One case with a total count of 20,000 had 70 per cent. and another with 30,500 had 75 per cent. of lymphocytes. Two cases with low total counts (boils with 3400 and streptococcus throat infection with 3600) had 82 per cent. and 62 per cent. of lymphocytes respectively. No reason for the substitution of lymphocytes for neutrophils could be found. Again, Michael Clarke [2] has reported a case of fatal septicæmia due to infection with B. pyocyaneus where the neutrophils were 51 per cent., lymphocyte group (chiefly large mononuclears) 46 per cent., total count 14,000.

Septicæmia—Septic Anæmia.—In conditions of generalised sepsis

[1] *Amer. Journ. Med. Sci.*, March 1913.
[2] *Med. Press*, 7th May, 1913.

or absorption of septic products in such affections as malignant endocarditis or puerperal fever the blood changes are profound. The blood as it exudes looks pale and watery. The plasma is often tinged with hæmoglobin. The fibrin network is increased. The number of red cells is diminished, and may fall to 1,000,000 per c.mm. The fall is often very rapid. We have known the numbers fall from normal to 2,500,000 on the third day after an operation, followed immediately by sepsis. A proportion of the red cells are often larger than in other forms of secondary anæmia, and may be larger than normal. This fact along with the hæmoglobinæmia would appear to suggest some dilution of the plasma. There is considerable diversity of size. Poikilocytosis is not a marked feature in acute cases but is very conspicuous in chronic forms.

There is generally a fair degree of diffuse polychromasia. Punctate basophilia, though often present, is not such a marked feature. Hæmoglobin is always diminished. The colour index may be very low, the average being about 0·6, but in acute cases it is higher, and tends to rise as the anæmia increases.

Normoblasts occur with some frequency in acute cases when the count has fallen below 2,500,000, but are rare with higher counts and in chronic cases. Megalolasts may be said not to occur. The large red cells which are found, and on whose presence the rise of colour index probably depends in great measure, do not attain the size of megalocytes, and the condition of the red cells should not lead to a mistaken diagnosis of pernicious anæmia. Even in the worst cases the colour index rarely rises above 0·8.

Leucocytes.—The number of leucocytes varies with the relationship of the infection to the resistance of the body. As long as the patient is not overwhelmed by the toxins there will be a leucocytosis. A high leucocytosis by no means indicates a favourable termination, but absence of leucocytosis or, more particularly, leucopenia in a severe case is a certain indication of a fatal prognosis. The leucocyte increase is caused by polymorphs. Myelocytes frequently appear, and are of grave significance as indicating that the powers of the marrow are becoming exhausted. The polymorphs show a definite glycogen reaction. Their neutrophil granules often stain with special intensity, but many, evidently degenerated, will be found in which both nucleus and granules stain badly.

Eosinophils are always diminished and often altogether disappear. Blood-plates are usually increased. In a large proportion of cases micro-

organisms may be cultivated from the blood, especially if it be examined in the early days of the disease.

Appendicitis.—Unless the condition extends to such a degree as to fall into the category of septicæmia, the red cells are not affected, beyond a trivial anæmia in long-standing cases. The condition of the leucocytes is of prime significance in diagnosis and prognosis, and as a factor in determining the advisability of operation.

In "foudroyant" cases and in all cases of great severity in which the patient is rapidly and intensely poisoned there is no leucocytosis and may indeed be a leucopenia. The polymorph proportion may be high, but it is not uncommon to find it between 60 and 70, or even lower. The glycogen reaction, however, is always very marked.

In slight catarrhal cases the count is rarely quite normal. There is usually a slight leucocytosis, perhaps 10,000 or 12,000. The polymorph percentage is not high, rarely above 75, and the glycogen reaction may be absent, doubtful, or very slight. In severer cases the range of the count is wide. The higher the count the more definite the indication for operation. Cases with a count of 20,000 or above rarely, if ever, deserve to escape operation, though they sometimes recover without it. Counts of 25,000 or anything above that indicate immediate operation in all cases. Gangrene, peritonitis, or suppuration are practically always present.

The great difficulty in utilising the leucocyte count in appendicitis lies in the fact that in the great majority of cases the count is about 15,000 to 17,000, even though the local condition is severe. The explanation of this probably lies in the character of the organisms concerned. They are usually those of the coli group, to which the body is more or less accustomed, and which do not cause a great marrow reaction. When the pus-producers are present in addition the reaction is generally greater. With counts of, say, 17,000 in the absence of definite signs or symptoms indicating operation or delay, weight should be given to the polymorph proportion and the intensity of the glycogen reaction. A polymorph proportion of 75 to 80 with a slight glycogen reaction would indicate a slight case, while a percentage of 85 or over with a marked glycogen reaction would mean a severe one. It is further to be noted that if the polymorph proportion and glycogen reaction seem to run counter to one another, more stress is to be laid as a rule on the polymorph proportion, for the organisms of the coli group, which are usually involved, do not cause so marked a glycogen reaction as the pus producers.

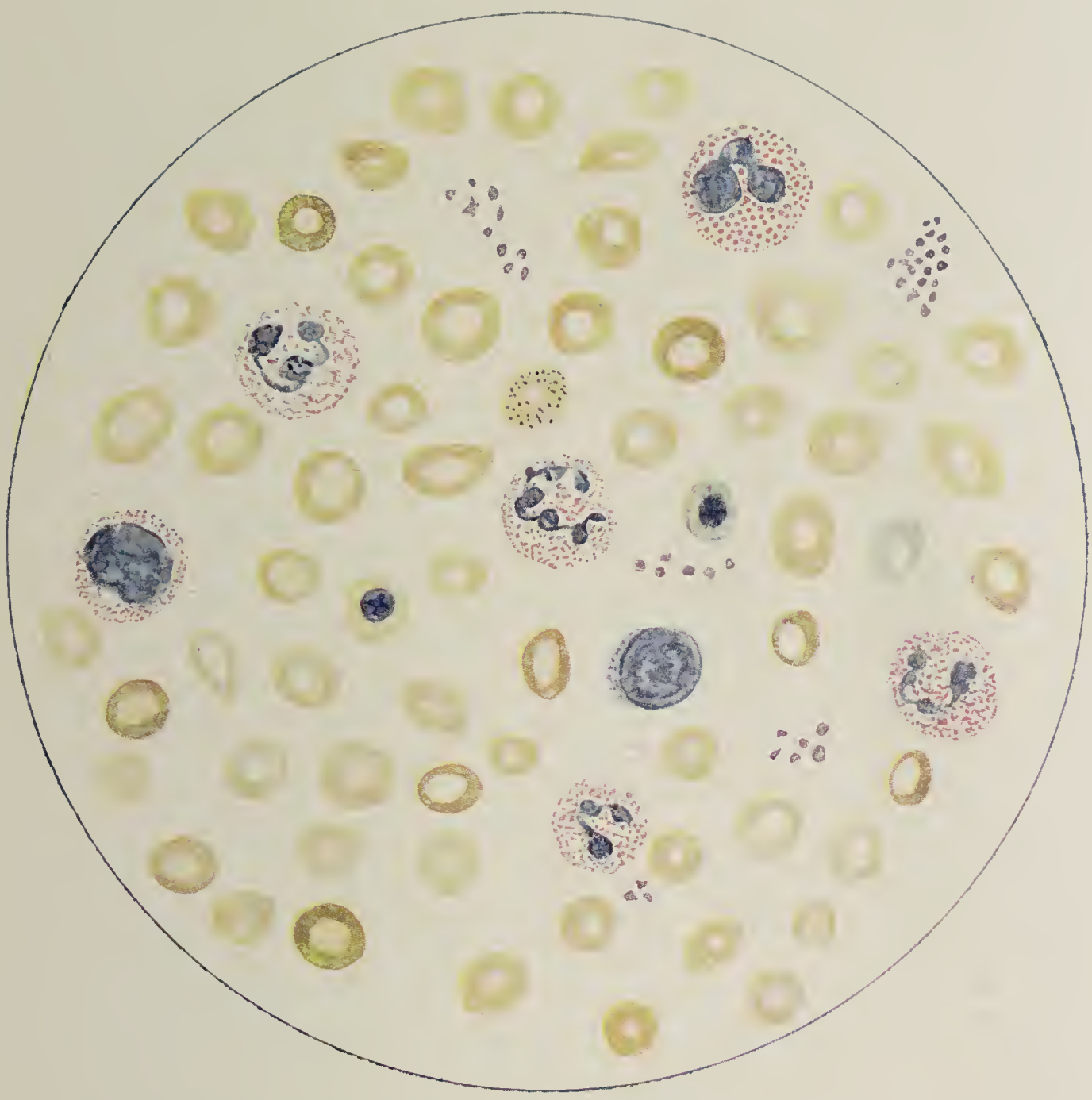


Plate XIV.—Severe Secondary (Septic) Anæmia from a Case of Ulcerative Endocarditis.

Red corpuscles are deformed and polychromasic. There are two normoblasts, one with marked polychromatophilia. One erythrocyte shows basophilic stippling.
Polymorphonuclear neutrophils are increased. One myelocyte is present.
Blood-plates are increased.

A. G., *fecit.*

If a single count is valuable, much more valuable is the result of repeated counts in individual cases. A rising count indicates an advancing inflammation, a definitely failing count, if the patient's condition be improving, means subsidence of the inflammation, but if the patient be worse, means that he is more poisoned, and generally that operation has been too long deferred. A stationary leuocytosis often means that an abscess is being walled off, and it must be remembered that in these cases the polymorph percentage may not be so high and glycogen reaction not so marked as one would expect them to be from the height of the count and from the patient's condition. In any case, however, a stationary leucocytosis may be taken as an indication for operation.

It must be understood that the foregoing only applies to cases in which there is clinically no doubt of the diagnosis of appendicitis. It must not be forgotten that acute catarrhal inflammations of the bowel may often cause a much higher leucocytosis than is usual in appendicitis, and that pyosalpinx may give rise to exactly the same changes in the blood as appendicitis, while all the bowel conditions which are likely to be mistaken for appendicitis, may sometimes cause leucocytosis. The blood-plates and fibrin network are increased.

Salpingitis.—What has been said about appendicitis applies to this condition. The leucocytosis may aid greatly in diagnosing a pyosalpinx from hydrosalpinx, ectopic gestation, or tubercle.

Abscess.—The leucocyte count is raised in all cases of septic abscess. The increase is purely polymorphonuclear. In a purely tuberculous abscess, leucocytosis, if it exists, is determined by a lymphocyte increase. When a septic abscess is opened the leucocytosis rapidly diminishes in most cases, but where acute inflammatory changes persist, as in many cases of whitlow, the leucocyte increase is correspondingly maintained. The leucocyte count with the glycogen reaction is an important guide to the efficiency of drainage.

Boil and Carbuncle.—The leucocyte count in these conditions is greatly increased and the polymorph percentage is correspondingly high. The glycogen reaction is intense.

Osteomyelitis.—Leucocytosis is generally considerable, and is of diagnostic value. Differential counts show the usual polymorph increase.

The occasional difficulty which occurs in diagnosing this condition from acute articular rheumatism can be avoided by examining the blood. In osteomyelitis the leucocytosis is usually higher than the 12,000 or 15,000 of acute rheumatism; the polymorph proportion is 80 or over; the glycogen reaction is marked. In acute rheumatism the polymorphs number as a rule less than 80 per cent. in uncomplicated cases, and the glycogen reaction is negative.

Otitis Media.—Darling[1] examined sixty-six cases. The average count in uncomplicated cases was 11,000, with 69 per cent. of polymorphs. With mastoid complication the average figures were 12,000, with 73 per cent. of polymorphs. No case without intracranial complication was found to have more than 86 per cent. of polymorphs, and no case with intracanial complication had a less percentage than 77. After operation there was generally a rise (average 8000) in the number of polymorphs. This passed off within four days. The glycogen reaction is present but as the presence of pus is not in doubt it is of little diagnostic value.

When there is any question of generalised infection or of the necessity or otherwise of tying the jugular vein, blood cultures may give results of great value.[2]

Gonorrhœa.—There is no very striking change in the blood in the ordinary acute cases. Leucocytes may be slightly increased, the increase affecting the polymorphs. In most cases there appears to be a slight increase of eosinophils corresponding with the invariable presence of eosinophils in the pus. In gonorrhœal septicæmia there is a polymorphonuclear leucocytosis, and in some of the few cases recorded the gonococcus has been cultivated from the blood.

Erysipelas.—In mild cases slight increase of polymorphs is the only change; in more severe cases the increase may be considerable. The range might be put at 12,000 to 20,000. The latter figure is rare. The count falls a day or two after the fever has subsided. A relapse is often preceded by a sharp rise in the leucocyte count. Eosinophils usually disappear. The fibrin network is increased, and there is some increase in the number of blood-plates.

Pleurisy—Pericarditis—Peritonitis.—The blood varies in accord-

[1] *Edin. Med. Journ.*, 1908.

[2] See Libman and Celler, *Amer. Journ. of Med. Sci.*, September 1909.

ance with many factors in these conditions. An acute rheumatic affection of any kind will bring about a polymorph leucocytosis, with an increase of fibrin and blood-plates. As already stated, a micrococcal infection will bring about similar changes, while a tuberculous condition will be associated either with no special blood change or with a lymphocytosis, relative or absolute. A dropsical effusion is not accompanied by any blood change. In acute infections the degree of leucocytosis is probably an index of the severity of the process, but gives no clue to the differentiation of the causal condition. The occurrence of a sharp rise of the leucocyte count in pleurisy may indicate that empyema has supervened. This will be practically certain if the glycogen reaction either appears or, if already present, becomes more intense.

CHAPTER XXXII

MALIGNANT DISEASE—WOUNDS AND FRACTURES—POISONS

Malignant Disease.—In early cases the usual blood-picture is simply a polymorph increase. In a fair number of cases there is merely an alteration in proportions, so that without increase in the total numbers there is a high polymorph percentage—a so-called "relative (polymorph) leucocytosis," or, more correctly, a diminished number of lymphocytes. In a smaller number of cases, especially in cachexia, there is increase of both neutrophils and lymphocytes, so that their proportions are not altered. A considerable number of myelocytes pass into the circulation in cancerous cachexia. Degenerative changes in the leucocytes are common. These include poor staining reactions of the polymorph granules and fraying of the edges of the lymphocytes with vacuolation of their protoplasm. Sooner or later anæmia supervenes. There is at first merely a diminution of hæmoglobin and consequent low colour index, then the red cells decrease and begin to exhibit degenerative phenomena, and the colour index tends to rise. The average size is reduced. There is anisocytosis and may be great deformity of the cells. Polychromasia becomes marked. Normoblasts and sometimes megaloblasts appear in the blood. Blood-plates are often fairly numerous. Fibrin tends to be diminished. There is often a slight amount of hæmoglobinæmia, and in advanced cases the glycogen reaction makes its appearance, probably due to secondary infection. In cachexia the leucocyte increase may be considerable. Cancer affecting internal organs is more likely to be associated with leucocytosis than cancer of external parts. Rapidly-growing tumours and tumours with metastases are more likely to be associated with leucocytosis than slow-growing or localised tumours. Enormous numbers of nucleated red cells may be present in cases of bone-marrow metastases. In this condition the blood-picture may closely resemble that of pernicious anæmia. Anæmia may become profound, megalocytes may be numerous, and the colour index may become high. Numerous myelocytes may make their appearance. As a rule there is leucocytosis, but this may fail. The diagnosis

from actual pernicious anæmia may then be very difficult. Pain and tenderness in the bones is generally greater than in pernicious anæmia.

Sarcoma as a rule causes more intense leucocytosis than carcinoma. In a few cases there is a very marked eosinophilia.

Cancer of the Œsophagus.—Owing to malnutrition there is more likely to be a diminution than an increase of white cells. Anæmia soon becomes established and acquires the features described above.

Cancer of the Stomach.—Before ulceration occurs leucocytes may be low as in other malnutritions. After ulceration, when hæmorrhage readily occurs, there may be very high counts, but one cannot depend upon these, as the factor of malnutrition seems to remain the predominating one. There is no definite information to be gained, therefore, from the blood in the diagnosis between cancer and ulcer. No condition is more frequently confused with pernicious anæmia (*q.v.*), as the anæmia resulting from malnutrition, cachexia, and hæmorrhage combined is often severe.

Cancer of the Liver and Pancreas.—There is always leucocytosis and the glycogen reaction. This fact often adds to the difficulty in diagnosis between cancer of the liver and inflammatory and suppurative processes in and about it. Cancer appears to interfere greatly with the function of the liver as a destroyer of intestinal toxins. They pass into the general circulation, probably cause the glycogen reaction and at least part of the leucocytosis, and very often give rise to fever.

Cancer of the Kidney and Suprarenal.—Leucocytosis is practically always present.

Cancer of the Uterus.—A slight leucocytosis may be present from the first. After hæmorrhages the counts may be high.

Cancer of the Breast.—As far as the blood is affected this may be considered as an external cancer, with little change in early cases. Advanced cases or cases with metastases show typical blood changes.

Mediastinal Lymphosarcoma.—In many cases leucocytosis is very slight or altogether absent. Its presence may be of great service in the differential diagnosis between solid neoplasm and aneurysm.

Significance of the Blood Changes in Cancer.—The anæmia and degenerative changes are to be regarded as a measure of the toxæmia, unless hæmorrhage is a marked feature. Blood regeneration is at a low ebb in cancer, and does not take place so rapidly or fully as in health. As a matter of practical diagnostic importance the examination of the blood in many cases gives disappointing results, but occasionally affords

positive evidence of great value. In the case of a deep-seated lesion leucocytosis will indicate in favour of suppuration or malignant disease rather than of one of the granulomata. The presence of a marked glycogen reaction would then distinguish suppuration from a comparatively early neoplasm. Eosinophilia might indicate the likelihood of hydatids, but is sometimes seen in sarcomata and fairly often in malignant ovarian disease. Leucocytosis, when present, is an important help in distinguishing between mediastinal tumour and aneurysm. A tumour being diagnosed, leucocytosis indicates a malignant rather than a simple type, and a progressive leucocytosis probably indicates a corresponding progress in tumour growth or metastasis. Digestion leucocytosis is often absent in cancer of the stomach and elsewhere, but this phenomenon is not constant, and may occur in other conditions.

Literature

Baradulin, *Folia Hæmatologica*, ix. 1 Teil, 1910, 407 (general account). Barrington and Kennedy, *Lancet*, 8th February 1913 (bone-marrow metastases).

Fractures—Wounds

Fractures.—In simple fracture there is a slight leucocytosis during the first three days, due to an increase of polymorphs and large lymphocytes. In compound fractures the blood changes are complicated by hæmorrhage and the nature of the wound.

Simon (*American Journ. of the Med. Sciences*, cxxxiii. 1907, 389) has published a remarkable case in which the typical blood-picture of myelocythæmia supervened in about a fortnight after a complicated fracture of the ankle. The spleen became palpable. A month after the injury the foot was amputated. The leukæmic changes were still present at the end of a week, but had altogether disappeared at the end of a month.

Wounds and Aseptic Operations.—After a wound or aseptic operation there is a leucocytosis, which appears in from six to twelve hours, and is independent of either anæsthesia or hæmorrhage, although the effects of these may be superimposed. Dawson[1] could not find any relationship between the degree of leucocytosis and the severity of the operation. In some aseptic cases he found a slight glycogen reaction, and suggested that the leucocytosis may be caused by micro-organisms, which it is impossible to exclude entirely. Busse,[2] on the other hand, found a very

[1] *Edin. Med. Journ.*, November 1905.
[2] *Archiv f. Gyn.*, lxxxv. 1.

distinct relationship between the degree of leucocytosis and the severity of the operation, but his higher counts were in cases of extensive abdominal or pelvic carcinomata. The increase is in the main polymorphonuclear, but the large lymphocytes may also increase to a less extent.

Drugs—Poisons—Anæsthetics

Hæmolytics.—A large number of substances act as hæmolytic agents. Their action is not in all cases the same.

1. There is a class which acts by dissolving hæmoglobin and liberating it from the corpuscles. Such substances are distilled water, glycerine, salts of the bile acids, snake venom, and the serum of animals either naturally or artificially antagonistic.

2. Another series of substances act as toxic agents to the red corpuscles, killing them but not necessarily leading to any escape of hæmoglobin from them. Examples of this group are phenyl-hydrazin, toluylen-diamine, pyrodin, amido-benzoic-ethyl-ether, pyrogallic and chromic acids.

The first group of substances causes the immediate appearance of hæmoglobin in the urine; the second group may cause blood-pigment to occur in the urine, but its appearance is delayed, and its amount is never comparable to that caused by the hæmolytics of the first group. All these substances also cause leucocytosis. A considerable number of substances which affect the white cells are referred to in the chapters on Leucocytosis. Such substances have been employed in experimental work,[1] but their effects are not likely to be met with in clinical cases.

Aniline, Nitro-benzene and its Compounds, Acetanilide, Phenazonum, and Phenacetin.—All these substances act in much the same way. In excessive dosage and in cases of idiosyncrasy there may be cyanosis, and the blood may appear chocolate coloured from the presence of methæmoglobin in the plasma. Anæmia results and is associated with an increase of polymorphonuclear cells. There may be a brief primary leucopenia. Eosinophils are diminished. There are the usual signs of secondary anæmia. Polychromasia is specially well marked, and nucleated red cells are numerous at first. A few myelocytes may be found. In cases which recover, regeneration of blood occurs very rapidly.

Salines.—It has been found that saline cathartics, especially if given in single massive doses, may concentrate the blood to such an

[1] See Noël Paton and Goodall, *Journ. of Physiology*, xxix. 1903, 411.

extent as to cause a definite increase of red corpuscles per cubic millimetre in the peripheral circulation.

Iodides.—There is an increase of the viscosity of the blood and a slightly greater number of polymorphs (Barenczik).[1]

Potassium Chlorate.—Poisoning may occur, especially in children. The red cells become broken down and tend to be agglutinated. Their size is rather increased. Basophilic staining is not marked. Polymorphs are distinctly increased, so that the total leucocytes per cubic millimetre may reach 20,000. The other forms of white cells tend to be diminished. The after-effects are the usual regenerative changes.

Lead.—Among lead workers it is not uncommon to find a very considerable increase in the number of the red corpuscles and an augmented hæmoglobin percentage. There may also be an increase of polymorphs. More commonly, however, the result of chronic lead-poisoning is an anæmia with special characters. While in the main the features are those of secondary anæmia, the anæmia is remarkable firstly for the large number of red corpuscles which show basophilic stippling. Polychromasia of the diffuse type is not nearly so common. The granular red corpuscles may amount to 10 per cent. in cases with severe symptoms. Another special feature of the blood in lead-poisoning is the large number of normoblasts which are found. They are much more numerous than in other secondary anæmias of equal severity. Cadwalader found that the number of stippled cells varies directly with the number of nucleated red cells. A small number of megalobasts make their appearance in severe cases. Leucocytes are increased in most cases, but not invariably.

Mercury.—In workers among mercury there may be a considerable increase of red corpuscles and of hæmoglobin, and leucocytosis. Anæmia frequently supervenes, and has pretty much the same characters as lead anæmia.

Silver.—Salts of silver and various combinations with silver have been found to cause after injection into animals a transient leucopenia, followed by polymorph leucocytosis, which in turn gives place to a lymphocytosis with eosinophilia (*Folia Hæmatologica*, vii. 1909, 76).

[1] *Folia Hæmatologica*, ix. ; *Zentralb.*, 1913, p. 25.

Phosphorus.—In chronic cases or in acute cases which survive there is first an increase of red corpuscles and a decided leucopenia. This is followed by a slight diminution of the red corpuscles and hæmoglobin, and some nucleated red cells appear in the blood. At the same time the leucopenia gives place to a moderate leucocytosis. The leucopenia is due to diminution of polymorphs, which have been found as low as 5 per cent.

Arsenic.—Arsenical poisoning gives rise to practically the same conditions. There may be increase of the red cells. This is followed by their diminution. The leucocytes may diminish, and later they increase. If the arsenic be continued there is a tendency for the lymphocytes to increase at the expense of the polymorphs. Atoxyl has given rise to similar effects.

Stockman and Charteris (*Journ. of Path. and Bact.*, ix. 1903) found that lead, mercury, and phosphorus first caused an increase of leucoblastic activity in the bone-marrow with a disappearance of fat. This was followed by anæmia, and later by gelatinous degeneration. Large doses of mercury did not cause the increase of red cells that has been found to follow the use of small doses.

Chloral Hydrate.—After the prolonged use or abuse of this drug anæmia with leucocytosis has been noticed.

Alcohol.—The changes vary. In many cases of delirium tremens there is a polymorph increase. The same finding is obtained in alcoholic multiple neuritis.

Quinine.—The hæmoglobinuria of blackwater fever has been attributed to the action of quinine, but this is not proved. Large doses cause leucocytosis. Stockman and Charteris found that it did not affect the bone-marrow.

Opium.—In acute poisoning the blood changes are due to cyanosis. In opium eaters the blood is not specially affected.

Colchicum.—Dixon and Malden (*Journ. of Physiol.*, xxxvii. 1908, 50) found that injections of colchicine caused a transient leucopenia, followed by a marked leucocytosis.

They found that colchicine caused a polymorph leucocytosis in carnivorous animals. In herbivora there was lymphocytosis, followed by neutrophil

leucocytosis. Large doses caused all the normal elements of the bone-marrow to be found in the general circulation. During maximum leucocytosis marrow cells were scanty in bone-marrow sections. During leucopenia the marrow was more cellular. Small doses of colchicine caused an increase of basophils without directly affecting the other leucocytes.

Felix mas and Senna.—These drugs have been found to cause an increase of polymorphs and a diminution of lymphocytes and eosinophils in worm infections. Leucocytosis after the administration of senna has been noted in other diseases (Grek and Reichenstein).[1]

Illuminating Gas Poisoning.—The red corpuscles are not destroyed, but are rendered physiologically useless in large measure by the fact that hæmoglobin forms a more stable compound with carbon monoxide than with oxygen. The individual corpuscles are said to be larger than normal in acute cases. We have not been able to confirm this in our cases. The red count is therefore at first unaffected, but if the patient survives it rapidly undergoes an increase, since regeneration is stimulated before the damaged corpuscles are eliminated. Leucocyte counts of from 15,000 to 30,000 have been found. The condition is readily recognised by the bright red colour of the blood and of the patient's mucous membranes, and a definite diagnosis can be made by means of the spectroscope in most cases.

Anæsthesia.—In the human subject it is difficult to obtain uncomplicated results. The common finding, however, which agrees with observations on animals, is that a polymorphonuclear leucocytosis follows anæsthesia by ether, while the leucocytes are unaffected by chloroform. Nitrous oxide and ethyl chloride have practically no effect.[2]

[1] *Wien. med. Woch.*, 1913.
[2] Guy, Goodall, and Reid, *Med. Press*, 1913.

CHAPTER XXXIII

DISEASES OF THE ALIMENTARY SYSTEM

Stomatitis.—The blood may be affected by the causal condition. In the simpler forms there is no change. In parasitic stomatitis there may be a slight leucocytosis, but counts in uncomplicated cases have been very seldom made.

Tonsillitis.—In acute cases the red cells are not affected. There is usually a high leucocytosis accompanied by the changes found in inflammatory conditions. In chronic cases there may be a secondary anæmia of some severity.

Obstruction of the Œsophagus.—Simple and malignant cases alike do not affect the blood until malnutrition causes a diminution of both red and white cells.

Gastritis.—In simple cases there is no change. In the severer cases the blood follows the ordinary course of inflammatory conditions in general.

Gastric Ulster.—There is always anæmia of secondary type, varying in degree. After hæmorrhage this may be very severe. In one case which recovered the red cells fell to 800,000 and the hæmoglobin to 5 per cent in two days. After hæmorrhage the leucocytes may of course be high, but ordinarily there is no increase, and there is often leucopenia.

Cancer of the Stomach.—See Chapter XXXII.

Duodenal Ulcer.—The changes are those found in gastric ulcer, but in cases occurring in men in middle life the anæmia may be trifling and of little help in diagnosis, as it may not exceed that resulting from chronic dyspepsia.

Enteritis and Colitis.—There may be a marked leucocytosis in severe acute cases, and this finding should not be taken as favouring a diagnosis of appendicitis unless the above conditions can be excluded. 25,000 is not an uncommon number. It is obvious that this gives valuable help in the diagnosis from typhoid. In chronic enteritis granular degeneration of red cells may be well marked, and there is sometimes a high percentage of lymphocytes with a normal total count.

Appendicitis.—See Chapter XXXI.

Constipation and Intestinal Obstruction.—The blood changes vary so much with the cause that they can hardly be grouped under this heading.

Diarrhœa.—In severe cases there may be high counts from concentration of the blood. The causal conditions may lead to alterations in the number or proportion of the white cells. In chronic cases there may be severe anæmia.

Sprue.—Anæmia is always a marked feature in the later stages of the disease, but in severe attacks it may be an early symptom. It is generally of the ordinary type of secondary anæmia, but in a fair proportion of cases there is a high colour index. Leucocytes, especially the polymorphs, are greatly diminished. Thin in his monograph on sprue refers to the severe anæmia which occurs, and its resemblance to pernicious anæmia. He quotes the following counts:—

Red Cells.	Hæmoglobin.	Colour Index.
1,820,000	70	1·9
2,500,000	58	1·1
2,000,000	65	1·6

In three cases of our own the counts were—

	Red Cells.	Hæmoglobin.	Colour Index.	White Cells.
(1)	2,280,000	65	1·16	4600
(2)	3,630,000	76	1·05	3800
(3)	4,480,000	90	1+	3800

In none of these cases were nucleated reds found, but the films, even that of case (3), were exactly like those of a mild pernicious anæmia in other respects, showing anisocytosis and poikilocytosis, fairly numerous megalocytes, polychromasia, and in (1) and (2) some granular basophilia

also. Lymphocytes were relatively in excess. Cases (1) and (2) recovered; (3) died suddenly of heart failure a few days after we saw him.

Intestinal Parasites

Eosinophilia is the striking feature of these infections, but is not constant. Speaking generally, our experience is that it is found in cases where the parasites are giving rise to symptoms, presumably by their toxins, and is absent when they are not.

Nematodes.—*Oxyuris Vermicularis.*—There may be slight anæmia. Eosinophilia is inconstant. Boycott[1] found a definite increase of eosinophils in two-fifths of his cases. Bucklers[2] has reported eosinophilia reaching 16 per cent.

Ascaris Lumbricoides.—Blood changes are uncommon. Eosinophilia may occur. Bucklers records a count of 19 per cent.

Ankylostoma Duodenale.—Only a small proportion of infected persons exhibit symptoms. When symptoms do occur the chief feature is anæmia. The degree of anæmia recorded by different authors varies considerably. This seems to indicate that there are degrees of severity among different outbreaks in different parts of the world. Boycott[3] regards the anæmia not as a true reduction of the number of red corpuscles but as a hydræmic plethora, a condition which Lorrain Smith holds to be the essential change in chlorosis. The average size of the cells is small, the colour index is low, anisocytosis is only moderate, normoblasts are infrequent, and megaloblasts rare. According to American authors the anæmia seems to be more severe in infections both with the old-world hook worm and its American congener. Red cells may fall below one million, and polychromasia may be marked. Poikilocytosis may be present, and normoblasts have been frequently noted. Boycott thinks that the poverty of the blood in hæmoglobin is proportionate to the number of worms. Leucocytosis is commonly present, especially in early infections, but when anæmia has supervened the leucocyte count may be diminished.

In nine-tenths at least of the cases there is eosinophilia. The percentage of these cells is commonly about 14, but much higher figures have been recorded. Lichtenstern found 72 per cent. in one case.

[1] *Brit. Med. Journ*, 1903.
[2] *Münch. med. Wochenschr.*, 1894.
[3] *Lancet*, 18th March 1911.

Boycott found the onset of eosinophilia after infection in two cases to be fourteen and twenty days respectively. When there is very severe anæmia the eosinophilia may fail.

Trichocephalus Dispar.—Infection is not associated with any blood change.

Trichina Spiralis.—When the muscles become invaded by the embryonic forms, leucocytosis is the rule. The increase is partly due to neutrophils, but eosinophilia is a very marked feature—60 per cent. has been recorded. This is, of course, of much importance in the diagnosis from enteric and similar conditions.

Cestodes.—In occasional cases of infection by *tænia solium* and *mediocancllata* there is anæmia. Eosinophilia and sometimes basophilia may be present.

Bothriocephalus Latus.—In some cases anæmia with features identical with those of pernicious anæmia may occur. It is said that this does not occur so long as the parasite is healthy, but that when it is diseased, or has died without being expelled, toxins are produced which give rise to the anæmia. The expulsion of the worm is followed by improvement or cure of the anæmia.

Tænia Echinococcus.—When the cystic stage affects man, a marked eosinophilia is the rule. Exceptions are common in our experience. Welsh and Barling[1] found eosinophilia in three-fourths of their cases, neutrophil leucocytosis exceeding 10,000 in 10 per cent. of cases, and a slight basophilia in 15 per cent.

Diseases of the Liver

Catarrhal Jaundice.—The serum is stained with bile. The bile salts are strongly hæmolytic, and this may account for the somewhat increased size of the red cells which is seen in cases of moderate severity. In mild cases the blood changes are practically *nil*. There is no leucocytosis.

Cholæmia.—In jaundice of long-standing, anæmia supervenes and may become fairly severe. Hæmoglobin is reduced to at least as great an extent as the red cells. The fragility of the red corpuscles tends to be diminished. In severe cases there may be some slight degree of leucocytosis.

[1] *Scot. Med. Journ.*, January 1907.

Gall-Stones.—The condition of the blood will fall into the condition described in one or other of the paragraphs immediately above where there is no inflammation. In cases where the passage of the gall-stone, or its entry into the common duct as a ball-valve, is attended with rigor and rise of temperature, there is a moderate leucocytosis, with a high percentage of polymorphs, and sometimes a definite glycogen reaction. In the ball-valve cases the local pain may be slight, the jaundice trivial, and they are apt to be mistaken for malaria. The leucocyte count should prevent this error.

Cirrhosis.—There is no essential change apart from that due to jaundice until nutrition is affected. Increasing anæmia of secondary type then supervenes. The white cell shows no marked change. Their numbers may be low, due to malnutrition, or may from time to time be increased, due to toxæmia, more particularly in the hypertrophic variety, and are increased after hæmatemesis or melæna. Rogers [1] in a series of Indian cases found a high leucocyte count to be an unfavourable sign.

Acute Yellow Atrophy.—This is not associated with anæmia, but there is a constant leucocytosis, of moderate amount—15,000 to 21,000.

Abscess of the Liver.—The red cells are not affected at first. In chronic cases there may be severe anæmia. There is generally leucocytosis. This is absolute in acute cases, but may be only relative in chronic cases with anæmia (Rogers). In acute hepatitis without abscess leucocytosis is nearly always absent, and may disappear towards the fatal termination of acute cases. There is said to be a very marked glycogen reaction in all cases, and the intensity of the reaction is an indication of the severity of the condition. The blood may give important indications in the diagnosis between this condition and malaria.

Diseases of the Pancreas

In acute pancreatitis there is usually a well-marked leucocytosis. In chronic pancreatitis leucopenia is the rule.

[1] *Lancet*, 10th August 1912.

Peritonitis and Ascites

Peritonitis and Tabes Mesenterica.—See Inflammation and Tuberculosis.

Ascites.—The blood changes depend on the causal condition. The ascites may *per se* have some effect. Thus ascites which is causing cardiac embarrassment may thereby give rise to artificially increased counts accompanying cyanosis. After tapping there may be a fall due to removal of cyanosis, but where cyanosis has not been a marked feature the counts may be increased after tapping from a rapid refilling of the abdomen with serum.

CHAPTER XXXIV

DISEASES OF THE DUCTLESS GLANDS

Spleen.—The great majority of the affections of the spleen are due to disease elsewhere, and there are very few primary diseases of the spleen in which the blood is affected.

Enlargement of the spleen may be due to the following causes:—

1. Infections, syphilis, tuberculosis, malaria, kala-azar, echinococcus, and the schistosoma of Japan.

2. Chronic intestinal affections in children, cirrhosis of the liver, acholuric icterus.

3. Pernicious anæmia, chlorosis, leukæmia, lymphadenoma, splenic anæmia, Gaucher's disease, splenic anæmia of infants, hæmochromatosis, splenomegalic polycythæmia.

4. Heart disease.

5. Waxy disease, sarcoma, rickets, wandering spleen.

Splenectomy.—A considerable number of cases have accumulated in which blood-counts have been carried out for prolonged periods after the operation. In most of these there has been transient enlargement of lymphatic glands, appearing any time up to eighteen months after operation. Eosinophilia (3 to 5 per cent. in persons whose previous numbers had been 0·5 or 1) may occur and persist for weeks or months. There is usually a slight lymphocytosis, which appears to be permanent as far as present observations go.

Lymphatic Glands.—Many of the affections of the lymphatic glands are not peculiar to these structures, although in some cases they may be the parts primarily attacked. Some gland affections are secondary to pathological conditions elsewhere. The blood changes are described in connection with the etiological or primary condition.

Myxœdema.—There is practically always anæmia, but its degree varies greatly. In slight cases the red corpuscles do not fall below 4,000,000 per c.mm., but in more advanced instances the number may be a million less. White cells are usually slightly diminished in number.

There is a relative lymphocytosis. The percentage of lymphocytes often exceeds 40. In several cases eosinophilia has been present, counts of from 4 to 10 per cent. having been recorded.

Cretinism.—Allowing for the peculiarities of the blood in children the changes are similar to those in myxœdema.

Exophthalmic Goitre.—Apart from those cases which are associated with chlorosis there is a certain amount of mild anæmia in about 50 per cent. of cases. The white cells may show no change, but in at least 50 per cent. of cases there is a very definite lymphocytosis, which may reach 60 per cent. in the differential count, while the average leucocyte count is increased to about 11,000. We have met with two cases followed by pernicious anæmia. One was a female, aged 45, who had suffered from exophthalmic goitre for twenty years. She had several attacks of anæmia from which she recovered. Most of the goitre symptoms disappeared, but eventually her red cell count fell to 1,150,000, hæmoglobin to 25 per cent., leucocytes to 1700, and the blood-picture was characteristic of pernicious anæmia. The other case, a female, aged 25, suffered from exophthalmic goitre. By the age of 30 the symptoms had given place to those of myxœdema. Soon afterwards pernicious anæmia with a red cell count of 1,500,000 supervened. This was followed by a short remission (red corpuscles 3,160,000, Hb 82), then a fatal relapse.

Acromegaly.—In a case in a young subject with giantism Sabrazès and Bonnes found a very slight degree of anæmia, a slight total increase of white cells (11,780), with a marked lymphocytosis (49 per cent.); while in an adult case without giantism there was a slight increase of red cells and hæmoglobin, a considerable reduction in the number of white cells, chiefly affecting the polymorphs, so that the most striking feature was a relative lymphocytosis. Dickson found slight basophilia (up to 2 per cent.) in four cases. In a case recently under our care the counts were—reds, 4,900,000; hæmoglobin, 85 per cent.; whites, 6800; with the proportions—polymorphs, 49 per cent.; lymphocytes, 48; eosinophils, 2; basophils, 1 per cent.

Addison's Disease.—There is generally some reduction in the number of red corpuscles, and the average count ranges from $3\frac{1}{2}$ to $4\frac{1}{2}$ millions, but it is not unusual to meet with cases showing anæmia of greater severity. In such cases some polychromasia and a few nucleated red cells may

be found. Hæmoglobin shows a reduction rather greater than the corresponding reduction of red corpuscles. It has been stated that methæmoglobin may be present in the blood in advanced cases. In a few instances an increase of red corpuscles has been found. We have only once met this. The patient, who had been living at a high altitude in Switzerland in search of health, had a count of 7,000,000, Hb 110. The count dropped to normal two weeks after his return to this country. The white cells are rarely increased in number. More frequently there is a slight diminution, chiefly affecting the polymorphs, so that a relative lymphocytosis is the usual finding. The number of eosinophils is usually increased. Percentages of 6 and 8 are not uncommon, and we have met with a case showing 10 per cent.

CHAPTER XXXV

DISEASES OF THE CIRCULATORY AND RESPIRATORY SYSTEMS

Diseases of the Circulatory System

Simple Endocarditis.—The blood changes vary with the cause. In the rheumatic cases there may be a leucocytosis of some intensity.

Malignant Endocarditis.—The blood changes are profound. They consist of the results of the toxæmic process which have been described in Chapter XXXI., associated, it may be, with changes due to the mechanical interference with the circulation brought about by incompetent valves or stenosis.

Chronic Endocarditis.—In this condition, described by Osler and Horder, there is a slowly progressive anæmia, without leucocytosis, but, as far as we are able to judge from the cases we have seen, with an increased proportion of polymorphs. Organisms are constantly found in the blood, usually streptococci of attenuated virulence, but the glycogen reaction is negative, as one would expect from the character of the infection.

Congenital Heart Disease.—High blood-counts are common. The red cells may number eight millions or more. The white cells are usually increased, but not to a corresponding extent. The hæmoglobin percentage is raised but the colour index is usually below unity, and the red corpuscles are often small, but rarely show much poikilocytosis. A count of eight millions would probably be associated with a hæmoglobin percentage of 120 or 130 instead of 160. The increase seems to be partly a compensatory process involving increased activity in blood formation and partly due to cyanosis and stasis.

Acquired Heart Disease.—Some high red counts have been recorded. The number of red corpuscles is not usually raised in fully compensated valvular disease, nor in aortic regurgitation with failure of compensation,

but it is usually above the normal in mitral disease when compensation has failed, and in many conditions of dilatation and chronic strain (emphysema, chronic bronchitis) without valvular disease, in which the compensation is inadequate.

Diseases of the Respiratory System

Adenoids.—There is practically always a certain degree of anæmia, characterised by diminished hæmoglobin rather than oligocythæmia. There is usually also some increase in the number of leucocytes, and the percentage of lymphocytes is commonly increased, as in all enlargements of lymphoid tissue in childhood.

Acute Bronchitis.—Leucocytosis occurs with some frequency but is not the rule. In those cases where the smaller tubes are involved and the question of possible pneumonia arises there is apt to be leucocytosis, so that the leucocyte count alone is not of great value in the diagnosis. The blood examination in other respects may, however, give important information (see Pneumonia).

Chronic Bronchitis.—In most cases the blood-picture is not disturbed. Occasionally, however, one meets with a case showing some increase of white cells. The explanation would appear to be that in these cases there is retention of secretion leading to absorption of septic products.

Asthma.—In a certain proportion of cases of true spasmodic asthma there is a great increase of eosinophil cells in the sputum and a definite increase of eosinophil cells in the blood. The eosinophilia appears a few hours before an isolated paroxysm and disappears rapidly after it, but in cases which are more continuous it may persist. The eosinophilia leads to a slight increase in the total count, and in a few cases it is accompanied by a moderate neutrophil leucocytosis. Little is known as to the explanation of the presence of eosinophilia in some cases and not in others. It does not occur in cardiac or renal asthma, or necessarily in those cases due to bronchitis or to latent tuberculous mischief in the lungs. It is almost always present in cases associated with nasal polypi, and the polypi themselves, and even the nasal secretion, may contain large numbers of eosinophils, but it is also found in cases with other nasal defects, such as œdema of the lower turbinates. Generally speaking, eosinophilic asthmas are those most likely to be benefited by treatment of the nasal passages.

Emphysema.—Just as in cases of cardiac failure, there may be an increase of blood-cells due to peripheral stasis in cases with cardiac dilatation. Eigers[1] found an increased volume of cells in proportion to plasma. This may be due to an increased number of red cells, but in some cases, especially in old people, he found that the volume of the individual red cells was increased. Eosinophilia has been noticed in a few cases, probably where the emphysema is secondary to asthma.

Bronchiectasis and Abscess of the Lung.—There is anæmia corresponding to the duration and severity of the affection, and an increase of white cells varying with the severity of the infection and the amount of absorption. As the blood changes in phthisis at a stage likely to be confused with these conditions are also due to sepsis, the blood does not help in the differential diagnosis. The glycogen reaction may be present, especially in cases where the discharge of pus is not free.

Phthisis.—See TUBERCULOSIS.

Pneumonia.—The blood shows changes of very great diagnostic and prognostic importance. A very striking change is the rapidity of coagulation time and the abundance of the fibrin network.

Ewart in a study of this subject (Edinburgh thesis, unpublished) found that there is a gradual shortening of the coagulation time up till the crisis, sometimes more abrupt just before it. After the crisis the coagulation time gradually returns to the normal for the individual. In cases subsiding by lysis the return of the coagulation time to normal is much more gradual. The coagulation time is not affected by variations in the temperature, by the actual number of leucocytes, or by the percentage of polymorphs. Ewart suggests a parallelism between the number of degenerated leucocytes and the coagulation time. He found that a coagulation time of less then one minute always betokened a fatal result.

In cases followed by empyema there is a lengthening of coagulation time after the crisis, followed by a second period of shortening during the acute stage of the empyema. The red cells may show an increase due to accumulation at the periphery in cases with cyanosis. The hæmoglobin and the specific gravity are correspondingly increased. There may be slight anæmia after the crisis.

White Cells.—The rule is an increased number of leucocytes. This

[1] Eiger, *Folia Hæmatologica*, vii. 1909, 233.

increase does not correspond either to the temperature or the amount of lung involved, but is rather the expression of the resistance of the patient to the toxin. While the phenomenon is of diagnostic importance, it is probable that it has even more value as a prognostic guide. Cases with slight symptoms may have no increase of white cells, but this very rarely occurs. In such cases there is usually a slight leucocytosis. On the other hand, cases with very severe symptoms may show no increase or more often a diminution of leucocytes. These are cases in which the tissues, including the bone-marrow, are overwhelmed by the toxin before they can react, and they are invariably fatal. In the great majority of cases there is an increase of white cells, ranging from 11,000 to 50,000 per c.mm. Our highest count has been 65,000, but a count of 100,000 has been recorded. Leucocytosis is generally found when cases first come under observation, so that it is probably present from the commencement of the illness. We have found it present within three hours from the initial rigor. There is little variation throughout the disease till a day or so before the crisis; the count then shows a tendency to fall in the favourable cases, but in some fatal cases the same thing is found. Although the leucocytes may have begun to diminish before the fall of temperature, they do not reach their normal number for several days after the crisis, and in cases ending by lysis their fall may be very gradual. When the leucocytes fall in number about the time of the crisis but fail to return to their normal number within three or four days we have an almost certain indication of some complication such as empyema, toxic nephritis, or pericarditis.

Differential Counts.—Up to the crisis there is an increase of polymorphs, which may constitute 95 per cent. of the white cells. A few myelocytes are almost invariably present in severe cases. Transitional cells and large lymphocytes are also increased absolutely though the percentage may be low. Small lymphocytes and eosinophils, on the other hand, are absolutely and relatively diminished. The latter may disappear altogether. After the crisis the polymorphs diminish while the large lymphocytes maintain their numbers for a day or two. The small lymphocytes and the eosinophils are gradually restored to their normal numbers. The persistence of eosinophils or their return before the crisis is a favourable element in prognosis. In the severe cases with a low leucocyte count the proportional relations between polymorphs and lymphocytes may remain unchanged, the polymorphs may be diminished or increased.

Leucolysis.—In no other disease, with the possible exception of

cancerous cachexia, is there so great a destruction of leucocytes in the blood. The degenerative changes may consist merely of vacuolation of the protoplasm. Both polymorphs and large lymphocytes are affected in this way. The more intense changes chiefly affect the polymorphs. The granules of the affected cells are less distinctly stained, and there may be considerable fraying or even disintegration of the protoplasm, while all degrees of karyolysis may be traced in different cells. These changes are more marked in the more severe cases.

Glycogen Reaction.—This is always present. It can be made out when cases first come under observation, but becomes rather more intense and affects a larger number of cells a day or two before the crisis. After the crisis the reaction remains for a few days and may be distinctly present after the leucocyte count has returned to normal. In the severe leucopenia cases the glycogen reaction is always intense, but if the polymorphs are diminished of course relatively few cells will show the change.

Blood-Plates.—The plates are always diminished in the blood up to the time of the crisis. After the crisis they are more abundant than usual.

Bacteria.—The diplococcus lanceolatus has repeatedly been cultivated from the blood. Those observers who have made cultures in a series of cases have found the cocci most frequently in severe cases or cases with general infection, so that the finding of organisms in any case may be regarded as a serious prognostic indication.

Significance of the Blood Changes in Pneumonia—Diagnosis.—The most important features are the decreased coagulation time, the leucocytosis, and the glycogen reaction. The diminished coagulation time would almost alone serve to distinguish pneumonia from any of the fevers with which it is the least likely to be confounded. In most cases the leucocyte count is greater than the initial counts of either tubercular meningitis or typhoid fever, and in neither of these conditions is a glycogen reaction to be found at the outset. The coagulation time and the glycogen reaction will help to distinguish pneumonia from bronchitis affecting the smaller tubes. In cases of acute pleurisy there may be a considerable leucocytosis, and in the rheumatic cases there may be considerable acceleration of the coagulation time, but the glycogen reaction is absent.

Prognosis.—Most help is obtained from the coagulation time, the total and the differential leucocyte counts, and the glycogen reaction, and especially in the relation of the last three factors to one another.

The coagulation time is of great importance. The more the time is accelerated the more grave is the prognosis. This will readily be understood when it is borne in mind that ante-mortem clotting is almost invariably found on post-mortem examination of cases of pneumonia. The leucocyte count is of very great importance. Severe cases with no increase or a diminution are doomed. It may be said that more cases die with under 13,000 leucocytes per c.mm. than with larger counts. In those cases with marked leucocytosis the actual numbers do not afford much information, except that high counts usually mean a severe case, but with good resisting power. When the usual fall after the crisis is interrupted a complication is practically certain. Provided that there is a sufficiently large total count, the percentage of polymorphs is not a matter of great importance, except that it is highest in the severer cases. The early appearance of myelocytes or of degenerated forms is a serious indication. The early absence of eosinophils indicates a severe case; their early return is one of the most favourable indications. The most favourable cases are those with a slight leucocytosis, say, 15,000 to 20,000, with a polymorph proportion not exceeding 80 per cent., and with a slight glycogen reaction. Of two cases with a count of 25,000 the more favourable is that with the lower polymorph percentage and the less marked glycogen reaction.

CHAPTER XXXVI

DISEASES OF THE SKIN, GENITO-URINARY AND NERVOUS SYSTEMS—GENERAL DISEASES

Diseases of the Skin

A small number of diseases of the skin affect the blood, but in most of them the changes are very inconstant in their incidence and degree.

In all skin diseases associated with much inflammation or ulceration a moderate leucocytosis may be expected, and in almost all chronic cases there is a slight eosinophilia of about 4 per cent.

Erythema.—A slight polymorph leucocytosis may be found. This is perhaps most constant in febrile cases of erythema nodosum.

Pemphigus.—Eosinophilia seems to be the rule in all varieties, and polymorph leucocytosis is almost constant. In P. foliaceus from 8 to 30 per cent. of eosinophils have been found, and in P. vegetans 15 per cent. has been recorded.

Dermatitis Herpetiformis.—Eosinophilia, sometimes intense, reaching 45 per cent. in some of our cases, is practically constant during the recurrent attacks, but usually disappears in the intervals. Eosinophils are found in large numbers in the vesicles before they break, but thereafter are often replaced by polymorphs.

Psoriasis.—In a few cases leucocytosis has been noted. The records of differential counts vary very greatly.

Lupus.—In tuberculous lupus anæmia is uncommon. In some ulcerative cases there has been a slight polymorph leucocytosis, in a few cases a slight lymphocytosis either relative or absolute as in other tuberculous infections, but in the majority of cases the blood is unchanged.

Pellagra.—In several cases there has been a slight increase of white cells with a high percentage of lymphocytes. A slight eosinophilia has also been found.

Mycosis Fungoides.—Slight anæmia with leucopenia, eosinophilia (4-8 per cent.), and more rarely a slight increase of basophils has been noticed.

Recklinghausen's Disease.—Gaillard[1] found a slight eosinophilia in a small proportion of cases.

Diseases of the Urinary System

Acute Nephritis.—A moderate degree of anæmia is usually present, and it may become severe. There is often a slight polymorph leucocytosis, with diminution of eosinophils at the outset. This is frequently noticed in nephritis occurring in the course of other diseases, *e.g.* scarlatina, in which leucocytosis may precede the nephritis, and in pernicious anæmia. Slight eosinophilia has been found to accompany the resolution stage.

Chronic Parenchymatous Nephritis.—Anæmia tends to become severe and hæmoglobin to be greatly diminished, so that the colour index may be low. The leucocyte count varies probably according to the amount of uræmic poisoning. As a rule the white cells are diminished.

Chronic Interstitial Nephritis.—There is not the same tendency to anæmia that exists in the parenchymatous variety, nor is leucocytosis common. In cases with signs of cardiac failure there may be increased counts due to peripheral stasis, and it should be kept in mind that hæmorrhage diminishes the red cell count while increasing the leucocytes, and that uræmia may lead to a leucocytosis of some importance.

Pyelitis.—As in other septic conditions, there is anæmia and polymorph leucocytosis. There are certain cases in which temporary blocking of the ureter occurs, caused apparently either by swelling of the mucous

[1] *Soc. de Biolog.*, lxi. 1906, 563.

membrane or by masses of pus or débris. Clinically this is often revealed by rigors and by a temporary diminution of the amount of pus in the urine. The blood always shows leucocytosis, with a more or less marked glycogen reaction. When the block ceases the leucocyte count drops and the glycogen reaction disappears. We have several times seen this condition mistaken for malaria in people who had lived in tropical countries.

Renal Calculus.—Any blood change which may occur will depend on hæmorrhage or pyelitis.

Cystitis.—There may be anæmia. Leucocytosis is usually absent, as there is no retention of septic products.

Bilharziosis.—There is a moderate secondary anæmia in most cases, which may become severe in cases where there is great loss of blood, secondary suppuration, and especially if there is chronic diarrhœa. There is a slight increase in the leucocyte count, eosinophils and large lymphocytes being increased and polymorphs diminished, at least relatively. The leucocytosis corresponds roughly in amount with the severity of the condition.

Diseases of the Reproductive System

Ovarian Cystoma.—In simple cysts the blood is not affected; in malignant or inflammatory conditions the blood follows the usual course in these conditions.

Septic and Inflammatory Conditions.—The blood changes follow the usual rules. Leucocytosis may be of great value in distinguishing septic mischief from ectopic gestation, hydrosalpinx, etc. The leucocyte count after operation gives a guide to the efficacy of drainage. In cases of pelvic exudation a high or increasing leucocytosis may indicate the presence of pus, in chronic pelvic abscess the leucocytes may not be much increased, but are likely to show the glycogen reaction.

Ectopic Gestation.—There may be a moderate leucocytosis. There is, however, no glycogen reaction and no increase of fibrin or increased coagulability. After hæmorrhage the diminution of red cells may

indicate the diagnosis, and there is a sudden increase of leucocytes. The anæmia is sometimes grave in itself.

Eclampsia.—Observations are very scanty. There is a definite leucocytosis as a rule, and the behaviour and indications given by the leucocyte count are practically the same as in septic conditions.

Myoma.—The blood-picture is negative in the absence of hæmorrhage, but prolonged menorrhagia from this cause may give rise to very severe secondary anæmia. The lowest count we had was reds, 2,600,000; hæmoglobin, 23 per cent.; whites, 6300, with a considerable number of normoblasts. At the end of a month of treatment with rest, iron, etc., the reds were 4,000,000, hæmoglobin 62 per cent. In such cases each menstrual flow causes a marked drop in reds and hæmoglobin. The question of surgical intervention is discussed on page 173.

Diseases of the Nervous System

Peripheral Neuritis.—The red cells are not affected. There may be some increase of leucocytes according to the cause. In alcoholic multiple neuritis there is a moderate increase of white cells in most cases, with an increased percentage of polymorphs.

Anterior Poliomyelitis.—There is generally a moderate leucocytosis during invasion in cases which begin acutely.

Spinal Scleroses.—In these diseases the blood is unaffected.

Meningitis.—See Septic Conditions and Tuberculosis.

Chorea.—Red cells are normal. There may be slight leucocytosis. Eosinophilia has been described, and this observation has been used as an argument to prove that chorea is not associated with rheumatism, in which eosinophilia does not occur. For some years we have examined the blood of all our cases of chorea but have not found eosinophilia to be even usual, much less constant.

Epilepsy.—Slight anæmia, chiefly affecting the hæmoglobin, may be present. There is often leucocytosis (10,000 to 18,000) in the intervals, and this greatly increases during the fits. A few cases

show eosinophilia. The almost constant leucocytosis has been used as an argument in favour of the toxæmic origin of the disease, and we have often found it useful in diagnosis in cases where the fits were badly described or doubtful in character.

Cerebral Hæmorrhage.—A moderate leucocytosis is the rule in recent cases.

Cerebral Tumour and Abscess.—The changes are the same qualitatively as in these conditions elsewhere, but are usually much less intense.

General Paralysis of the Insane.—There is a moderate and progressive anæmia, involving chiefly a diminution of the hæmoglobin. In the first stage there is a polymorph leucocytosis which may show exacerbations at intervals. In the second stage there is generally a reduction of the polymorphs and at least a relative increase of lymphocytes, especially of the large forms. The polymorphs, however, are increased at intervals, and there is slight eosinophilia from time to time. In the third stage the polymorphs diminish considerably and lymphocytes show a corresponding increase.

During convulsive seizures there is usually a sudden and great increase of polymorphs and a smaller increase of large lymphocytes. Myelocytes may also appear in considerable numbers.

Mania.—In practically all forms of excited insanity there is a polymorph leucocytosis, which increases with exacerbations. In delirium tremens and continuous alcoholic mania there is leucocytosis. Puerperal mania often shows leucocytosis, but this is not constant. Eosinophilia (up to 8 per cent.) is not uncommon.

General Diseases

Diabetes Mellitus.—In early cases as long as the patient is in comparatively good health the number of red cells tends to be rather high, with a corresponding increase of hæmoglobin. The counts are apt to be disturbed by changes in osmosis disturbing the balance between blood and tissue fluids. In cachetic cases there is anæmia. Certain special staining reactions in the red cells have been described;[1]

[1] Bremer, *New York Med. Journ.*, 7th March 1896. Williamson, *Brit. Med. Journ.*, 19th September 1896.

they are of no practical value. The "extra-cellular" glycogen is increased. The white cells are practically unaffected as regards numbers. Von Limbeck states that there may be an unusually large digestion leucocytosis. In diabetic coma red cell counts may be high from cyanosis. The glycogen reaction becomes positive, and there is usually a leucocytosis. Lipæmia has already been discussed (p. 191).

Acute Rheumatism.—There is a remarkable increase in the fibrin network, but the coagulation time is not more rapid than usual. Red cells are nearly always diminished, but rarely fall below 4,000,000. Hæmoglobin is reduced. White cells are always increased, but very rarely reach or exceed 20,000. 12,000 to 15,000 is the usual count in uncomplicated cases. The glycogen reaction is absent, a point which may be of considerable diagnostic value. Organisms are not usually found.

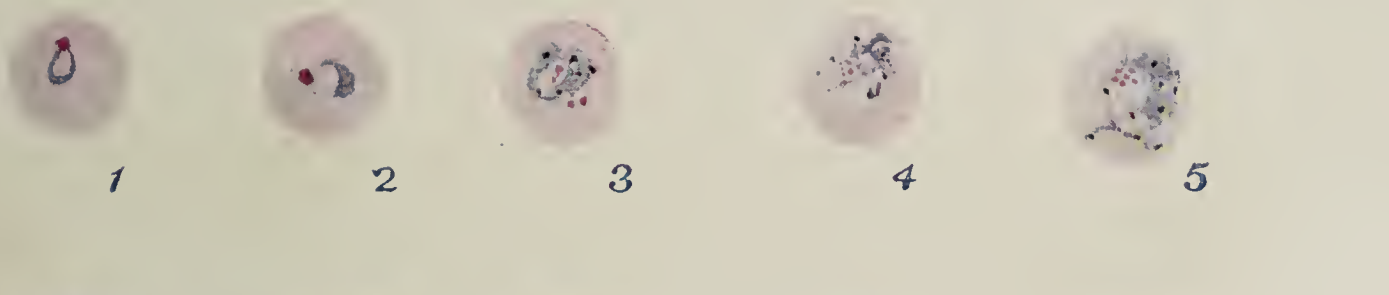
Chronic Rheumatism.—The blood is unchanged.

Rheumatoid Arthritis.—In their study of forty-two cases Bull-more and Waterhouse found a slight degree of anæmia to be almost always present. Except for the occasional appearance of a few myelocytes the white cells were normal.

Gout.—In acute attacks fibrin is increased. As in other conditions in which there is an excess of purins (endogenous or exogenous) in the blood, uric acid can frequently be separated from the serum by means of the thread test. Red cells are not affected except in long-standing and severe cases, which may be anæmic. Leucocytes are usually unaffected, but may be slightly increased in acute attacks.

Rickets.—Anæmia is frequently associated with rickets, but should probably be regarded as a consequence of the common cause rather than a result of rickets *per se*. In a recent series Finlay found a complete absence of signs of anæmia in uncomplicated cases, but there was some variation in the size of the red cells. Enormously large leucocyte counts have been recorded, but these are to be regarded as the result of complications. Having due regard to the age of the patients, it is difficult to say that the leucocytes show any abnormal features.

Osteomalacia.—The various statements regarding changes in the reaction of the blood have not been authenticated. Pappenheim and others have examined the cells with negative results. In the later stages there may be anæmia and leucocytosis, both very slight. Eosinophilia has been described, and in a case under our care the eosinophils were constantly about 5 per cent.



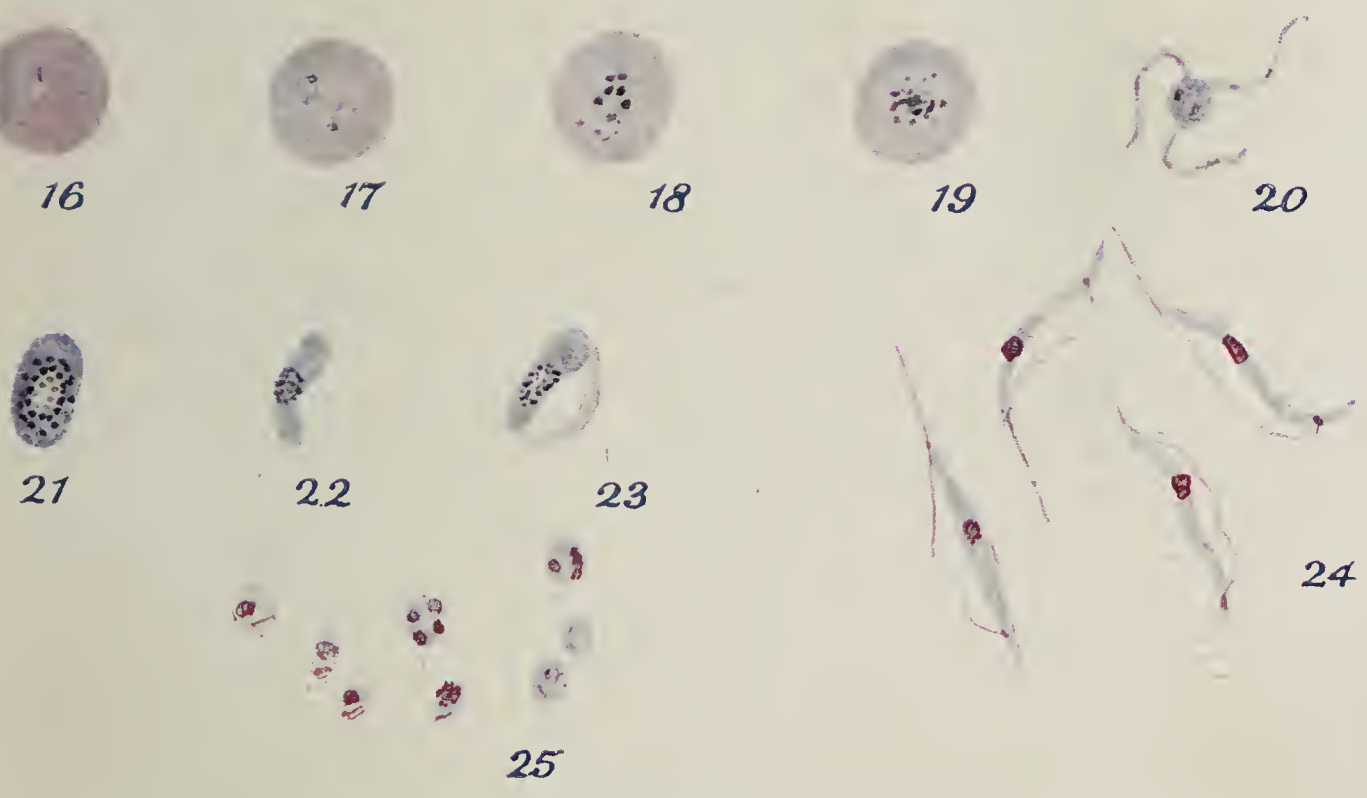


Plate XV.—(Leishman's Stain).

Figs. 1-10.—Tertian Malarial Parasites.

1-6. Trophozoites.
7. Schizont.
8. Macrogametocyte or female.
9. Microgametocyte or male.
10. Segmenting form.

Figs. 11-15.—Quartan Malarial Parasites.

11, 12. Trophozoites.
13. Macrogametocyte.
14. Microgametocyte.
15. Segmenting form.

Figs. 16-23.—Estivo-Autumnal Parasites.

16, 17. Trophozoites.
18, 19. Schizonts.
20. Flagellated form.
21. Microgametocyte or male.
22, 23. Macrogametocyte or female.

Fig. 24.—Trypanosoma Gambiense.

Fig. 25. Leishman-Donovan Bodies.

A. G., *fecit.*

PART V

DISEASES DUE TO ANIMAL PARASITES IN THE BLOOD

CHAPTER XXXVII

MALARIA OR AGUE

Definition.—A specific febrile disease caused by the introduction into the blood of protozoal parasites by the agency of mosquito bites.

Distribution.—Malaria is widely distributed throughout the world. It is found throughout Africa, except in parts of Cape Colony, and throughout Asia. It occurs in West Australia and the Polynesian Islands, in most of South America, parts of the United States, and in Canada about the northern shore of Lake Ontario. In Europe there are probably endemic centres in all the countries except Great Britain and Norway. The distribution may vary considerably in the course of a few years. A series of wet seasons may greatly extend the distribution of the disease, and dry seasons or antimalarial measures may curtail it.

Etiology.—Malaria is caused by the parasites Plasmodium vivax, which gives rise to tertian malaria; Plasmodium malariæ, which gives rise to quartan fever; and Laverania malariæ, which gives rise to æstivo-autumnal fever or subtertian malaria. The parasites are introduced into the blood by the bite of an anopheline mosquito. Anopheles maculipennis is perhaps the most common cause of malaria in Europe, but at least twenty members of the anopheles family are known carriers of the disease. Only the female mosquito sucks blood and transmits the infection.

Life-History of the Parasite

A. *In Man—Schizogony.*—In the cells and ducts of salivary glands of infected insects parasites are found in the form of fusiform bodies, measuring about $15 \times 1{\cdot}5\ \mu$ (Fig. 15). These bodies consist of cytoplasm with a chromatin nucleus and are known as *sporozoites*. When the

mosquito bites man he is inoculated with these sporozoites, which invade the red blood corpuscles and develop into small parasites called *trophozoites.* These trophozoites (Plate XV., 1, 2, 3) increase in size, and by the formation of a vacuole become ring-shaped. They throw out pseudopodia and continue to grow, producing a pigment of excrementitious nature, which accumulates in the form of granules. When fully grown the trophozoite loses its power of amœboid movement, becomes spherical and full of pigment granules. It is now known as a *schizont.* The parasite next breaks up into segments, each containing a portion of nuclear chromatin. The segments or spores are known as *merozoites.* A residual mass containing the pigment is left unsegmented. The blood corpuscle now breaks up. The merozoites are liberated and some of them, as well as the residual mass and pigment, are taken up by leucocytes and destroyed. The merozoites may again enter blood corpuscles and start again as trophozoites, thus completing an asexual cycle—the cycle of Golgi (Fig. 27, Cycle *a*). The repetition of this process leads to a multiplication of the parasites, and each rupture of a corpuscle allows the liberation of toxins, so that in the course of perhaps eight to ten or twelve days (*the incubation period*) the collective toxin is sufficient to determine an attack of fever.

The earliest form of sexual parasite is like an ordinary merozoite, but it grows more slowly, never develops a vacuole, and becomes a *crescent.* The crescent may be heavily pigmented and granular and is distinguished as a female (*macrogametocyte, female sporont*), or may be lighter and clearer and is then differentiated as a male (*microgametocyte, male sporont*). The macrogametocytes possess a small rounded nucleus, poor in chromatin and placed eccentrically, and a granular and pigmented cytoplasm (Plate XV., 8). They are tenacious of life, and as the result of a chill or diminished health in their host they may sporulate and the merozoites may again invade fresh blood corpuscles (Fig. 27, Cycle *f*). This would account for attacks of malaria months or years after infection.

A different view is, however, held by Thomson,[1] who maintains that crescents die in the peripheral blood in a few days, and that fresh breeds come into the circulating blood as the result of replenishment from surviving asexual forms in the internal organs, chiefly the bone-marrow and spleen. Thomson also holds that there is not sufficient evidence to support the view that crescents are able to revert back to the asexual phase.

[1] *Annals of Trop. Med.*, viii. 1914, p. 85.

The microgametocyte is characterised by a large nucleus, extending like a band across the protoplasm, with abundant chromatin, clear protoplasm, and less pigment than the female (Plate XV., 9). The macrogametocyte and microgametocyte are the means of propagating the parasite in the mosquito, and, unlike the female bodies, if the microgametocytes fail to reach the intestine of the mosquito they die off (Fig. 27, Cycle *m*).

It has been customary to regard the malaria parasite as intracorpuscular. Mary Rowley-Lawson[1] maintains that it is extracorpuscular during its entire developmental cycle. The parasite attaches itself to the corpuscle by means of thread-like processes. Other pseudopodia form a loop on the surface of the corpuscle, and squeeze up the portion of the corpuscle within the loop into a conical mound. When viewed from the surface the pseudopodia give the characteristic ring-form appearance. The portion of corpuscle within the pseudopodia loses its hæmoglobin and gives rise to the "achromatic zone."



FIG. 27.—LIFE-HISTORY OF THE MALARIA PARASITE.

a. The asexual cycle in man. *f*. the female cycle in man. *m*. The male cycle in man. f^1, m^1. Female and male gametes which conjugate in the mosquito to form a zygote—the oökinete. This forms an oöcyst, different stages of which are shown under the epithelium of the stomach of the mosquito. Eventually the oöcyst develops sporoblasts which become sporozoites. When the cyst ruptures these reach the salivary glands and from there may be passed into the blood of man.

Plasmodium Vivax — The Tertian Parasite. — A sporozoite or merozoite attacks a red corpuscle and gives rise to a trophozoite which is at first about one-third of the size of the corpuscle. It grows rapidly, acting deleteriously on the corpuscle, which becomes pale and

[1] *Journ. of Exp. Med.*, xvii. 1913, p. 374.

swollen and may show, after staining with a Romanowsky dye, the presence of red granules called Schüffner's dots. In about thirty hours the parasite becomes rounded to form a schizont, and may measure 8·5 μ in diameter. From the thirtieth to the forty-eighth hour the schizonts form from fifteen to twenty merozoites, the pigment being packed at the periphery or, more commonly, at the centre. The red corpuscle is now greatly swollen and almost colourless. About the forty-eighth hour the remains of the corpuscle disappear and the spores escape. The spores measure 1·5 μ.

Characters of the Different Malarial Parasites

	Plasmodium Vivax.	Plasmodium Malariæ.	Laverania Malariæ.
Schizogony completed in	48 hours.	72 hours.	48 hours or less.
Young trophozoite	Large, very motile, long pseudopodia.	Intermediate in size, movements slow, pseudopodia short.	Small, motile.
Schizont	Larger than red corpuscle.	Smaller than red corpuscle.	Much smaller than red corpuscle.
Pigment	Fine, motile.	Coarse, movement sluggish, often peripheral, brownish.	Fine, scanty, often non-motile.
Merozoites	15-20 arranged regularly.	6-12 arranged in a rosette.	8-15 arranged irregularly.
Gametocytes	Resemble schizonts.	Resemble schizonts.	Crescent.
Red corpuscles	Pale and swollen	Practically unaffected.	Often small and dark.

Plasmodium Malariæ—The Quartan Parasite.—The young trophozoite is smaller than that of Plasmodium vivax. It shows little protoplasmic activity, and soon begins to produce pigment in the form of short rods. After twenty-four hours the parasite is larger and the pigment is more abundant. The pigment is very dark in colour, non-motile, tends to accumulate at the periphery, and appears earlier and is more obvious than in the other forms. The infected red corpuscles may not be much altered, or may become rather smaller and darker in colour. In about sixty hours the trophozoite becomes a schizont, which is a round pigmented body surrounded by the remains of a red corpuscle. During the next twelve hours the nucleus breaks up into six or twelve masses which, with surrounding cytoplasm, form spores. The pigment is arranged in the centre, giving the whole parasite a daisy-like appearance. The merozoites, measuring 1·75 μ, are now set free and are either killed off or re-enter blood corpuscles. The

whole process of sporulation takes place in the peripheral blood and occupies seventy-two hours.

Laverania Malariæ—The Æstivo-Autumnal Parasite.—The young trophozoite is exceedingly small. It soon assumes a delicate ring shape, and measures about 1 μ in diameter. It grows into an oval form, which becomes pigmented. The red corpuscles may degenerate, some of them acquiring a curious brassy appearance, and others, in specimens stained by Leishman's method, showing large irregular red streaks or dots, known as Maurer's dots. The full-grown schizont measures 4·5 μ. It is very rarely seen in the peripheral blood. Segmentation takes place in the spleen and other organs. The merozoites number eight to fifteen and measure 0·7 μ. Schizogony is completed in from thirty-six to forty-eight hours.

The gametocytes differ in shape from the schizonts. They are characterised by being crescent-shaped, and usually show the remains of a red cell stretched round them.

The macrogametocyte is long and thin and has comparatively dark-coloured cytoplasm. The chromatin is compact and is surrounded by pigment. The microgametocyte is shorter and broader. The protoplasm is more hyaline, the chromatin more diffuse, and the pigment more scattered. Flagellated forms are sometimes seen in specimens of blood, but such forms are properly part of the life cycle in the mosquito. Possibly their occurrence in films is determined by exposure to air or artificial conditions. They may be brought out by adding water to the blood.

It is to be noted that it is common in any type and in any case in which the parasites are numerous to find two plasmodia in a single corpuscle.

B. *In the Mosquito—Sporogony.*—If the female mosquito in her search for nourishment for her eggs sucks blood from a person whose circulating fluid contains macro- and microgametocytes, a sexual cycle of the parasite's life-history begins. The macrogametocyte undergoes reduction by division of its nucleus and formation of polar bodies. It is now known as a *macrogamete* (Fig. 27, f^1). The microgametocyte undergoes a somewhat similar change. It throws out four to six thread-like protoplasmic projections. Chromatin masses separate from the nucleus and pass into these threads in the form of dots and bars. These flagella-like bodies lash about vigorously, then break off, and are known as *microgametes* (Fig. 27, m^1). A microgamete now conjugates with a macrogomete and the male and female pronuclei fuse and form a zygote—the *oökinete.*

The zygote elongates and its anterior extremity becomes pointed. It now pierces the epithelium of the mosquito's stomach and under the epithelium forms a thin-walled cyst—the oöcyst. This cyst grows rapidly, the nucleus divides to form a large number of daughter nuclei which, with their surrounding protoplasm, form the *sporoblasts*. The sporoblast nuclei further divide and pass into projections of the cytoplasm. Each of these projections with its chromatin particle is a sporozite. Eventually the oöcyst bursts into the cœlom of the mosquito and the sporozoites enter the blood-stream and are carried all over the insect's body. Finally they find their way to the salivary glands, where they are ready to infect a new host. Possibly they may be carried by the eggs to a new generation of mosquitoes.

Conditions Favouring Infection.—The most important condition favouring infection is residence in a malarial district. By that we understand a district where there are infected persons carrying gametocytes in their blood, where there are mosquitoes capable of carrying the parasite, and where the climatic conditions are favourable to the growth of the parasite in the mosquito. A temperate or warm climate is thus essential as well as moist or marshy areas for the development of the mosquito. A wet season may therefore be an important predisposing cause.

Fœtal malaria may occur, but is exceedingly rare. Children, being more exposed to mosquito bites, are specially liable to infection. Occupation may play a part in subjecting persons to increased risk of infection.

Conditions Favouring Development of the Parasite after Infection.—Attacks of malaria appear to confer a certain degree of immunity. Natives of a malarial district are less subject to the disease than immigrants. Lowered conditions of health from any cause—starvation, chills, or chronic ailments—appear to diminish the resistance of the body to the development of the parasite.

Pathology.—The parasites by their growth cause destruction of the red blood corpuscles and at the same time liberate toxins which are capable of causing fever and a certain degree of hæmolysis. The quartan parasites, until they sporulate, do practically no damage to the red corpuscles, and thus sporulating forms are readily found in the peripheral blood. The tertian and æstivo-autumnal forms, on the other hand, markedly affect the red corpuscles they inhabit, and therefore these are arrested by the endothelium of the internal organs, particularly the

spleen, bone-marrow, and liver. Sporulating tertian forms are thus rare in the peripheral blood, and sporulating æstivo-autumnal forms are very rare. The latter parasite may bring about serious damage by causing red corpuscles to agglutinate and form thrombi in the vessels of the brain or internal organs. During sporulation the parasites liberate pigment, which becomes deposited, sometimes in large amount, in the organs where sporulation occurs. It is also taken up by the leucocytes, and may be carried throughout the body. During sporulation toxins are liberated. It follows that the paroxysms of fever are determined by this phase of the life-history of the parasite. The red corpuscles destroyed by the parasites, mechanically and chemically, set free a considerable amount of pigment which is found as hæmosiderin, most abundantly in the liver, but also in the spleen, kidneys, and bone-marrow. Death from either quartan or simple tertian malaria is very rare. The pathological findings include the presence of parasites, malarial pigment, and blood-pigment in the organs, enlargement of the spleen, and the conditions usually associated with a toxic febrile affection.

In æstivo-autumnal fever the lesions found may be more severe. The skin may show a yellowish colour. The intestines may be pigmented and inflamed, the liver enlarged, soft, and dark in colour. Its capillaries are dilated, and their endothelium is swollen and pigmented. The liver cells are compressed and may be necrosed. They contain iron-pigment. The spleen is enlarged, the capsule is tense, the pulp is soft, the red cells contain schizonts and crescents. Pigment is present in large lymphocytes and endothelium. The kidneys show pigmentation of the capillary walls, and parasites are common in the intertubular capillaries. Varying degrees of nephritis may be found. The bone-marrow may show an extension of hæmopoietic tissue from the extremities towards the centre of the shaft of the long bones. It is always pigmented and rich in parasites.

In chronic malaria and malarial cachexia there are cirrhotic changes in the organs, and the spleen and liver may be greatly enlarged. The bone-marrow may become sclerotic or gelatinous. Parenchymatous nephritis and waxy disease sometimes supervene.

Symptoms.—The symptoms caused by the three parasites have a general resemblance, but the course and severity of the different fevers vary considerably.

1. Symptoms due to Plasmodium Vivax

(a) *Simple Tertian Fever.*—Simple tertian fever is characterised by paroxysms of fever occurring every forty-eight hours and separated by an interval corresponding to the length of time taken by the parasite to develop from the merozoite to the fully-developed schizont.

Prodromata.—Prodromal symptoms may be absent but certain symptoms may arise from sporulation of parasites not numerous enough to cause fever. These symptoms include great lassitude and weakness, headache, and pains in the back, extremities, and joints. Treatment at this stage may abort an attack. In any case symptoms will have disappeared on the following day. If untreated the patient will probably show febrile symptoms on the next day. The attack may begin at any time, but frequently starts in the early morning. Symptoms are usually ushered in by an attack of nausea or vomiting, and there may be a slight rise of temperature. The cycle of events is then a cold stage succeeded by a warm stage and a sweating stage. In children the paroxysm may be ushered in by convulsions, and the cold stage and sweating may be absent.

The cold stage is associated with an actual feeling of chilliness and marked rigors. The shivering may shake the patient's bed. His teeth chatter, his lips look blue, and goose-skin may be noticed. During this stage the temperature is steadily rising, and in spite of the outward manifestations of cold the rectal temperature may reach 104° or 105° F. In from ten to twenty minutes this phase has passed.

The warm stage begins with fleeting sensations of warmth, which, at first, are rather welcomed by the patient. They increase in intensity and duration, and soon the patient is uncomfortably hot. The temperature may continue to rise. The mouth is dry, and herpes may appear on the lips. Vomiting, and more rarely diarrhœa, may occur. The spleen is enlarged and tender and a soft murmur may be heard over it on auscultation. The pulse is rapid, its volume is large, and the dicrotic wave may be palpable. A temporary soft systolic cardiac murmur is sometimes audible. A slight cough may be noticed, and rhonchi and coarse crepitations may be detected. The skin is hot and dry. Skin eruptions sometimes occur; they are usually urticarial or erythematous. The skin and conjunctivæ may show a yellowish tinge. The headache and pains in the limbs generally increase. This stage may last as long as five hours.

Sweating Stage.—A gentle perspiration is rapidly followed by profuse

sweating all over the body. The sweat has a characteristic odour. The pulse, respirations, and temperature fall to normal in about four hours. The patient generally falls asleep and awakens feeling comparatively well but somewhat weak.

In the apyrexial interval, which lasts about thirty-six hours, the patient's temperature may be subnormal. The blood shows developing parasites and various changes in the cellular elements, to be described later. The fæces show an increase of iron and bile products. During the attack the urine is at first increased in quantity. It is dark coloured and very acid in reaction. Nothwithstanding the increased quantity, the specific gravity is increased, due to more rapid metabolism and a consequently greater output of solids. Nitrogen, chlorides, and sulphates are increased. Phosphates are diminished during the attacks. Urobilin may be increased. Albuminuria sometimes occurs. The diazo-reaction is occasionally obtained. During the intermission the quantity of urine falls, but there is still an increased output of solids. The output of phosphates is now increased. Sulphates remain abundant. Chlorides are diminished. Iron is markedly increased.

During convalescence there may be very marked polyuria.

Course.—Tertian malaria tends towards a spontaneous cure after several paroxysms. The incidence of the attacks varies both as regards severity and time. Anticipating attacks sometimes occur. In these there is a shortening of the apyrexial interval. Lengthening of the interval is referred to as retardation of the attacks, and is generally due to the exhibition of quinine, but may be due to weakening of the parasite from some other cause.

(b) *Double Tertian Fever.*—This condition is due to infection with two broods of parasites which mature on different days. As sporulation of one or other occurs every day, the result is a quotidian fever. As a rule the attacks begin at the same time each day, but the attack due to one brood may be later than the other. The attacks may not be of the same severity, but if untreated the weaker tends in time to equal the more severe. In a double infection the duration of the individual paroxysm is usually shorter. Double tertian fever may also arise through anticipation of a simple tertian infection.

(c) *Irregular Tertian Fever.*—Different broods of parasites may sporulate at different times on the same day, and an almost continuous fever may result.

2. Symptoms due to Plasmodium Malariæ

(a) *Simple Quartan Fever.*—A paroxysm occurs every seventy-two hours.

Prodromata.—Prodromal symptoms are the rule, and are similar to those found in tertian fever.

The cold stage lasts from fifteen to thirty minutes, and if the blood be examined sporulating forms and young forms of the parasite may be found.

The hot stage lasts from three to six hours.

The sweating stage lasts a few hours.

Course.—Quartan fever has a special tendency to relapse. The febrile paroxysm and resulting anæmia may be severe, but the parasite does not multiply in sufficient numbers to cause pernicious symptoms, and does not accumulate in internal organs in sufficient numbers to cause serious local disease.

(b) *Double Quartan Fever.*—This condition is caused by two broods of parasites inoculated on different days. The attacks of fever occur on two successive days, followed by a remission of twenty-four hours. The attacks caused by the different broods are not always of the same intensity.

(c) *Triple Quartan Fever.*—This is caused by three broods of quartan parasites coming to maturity on three successive days. The result is a quotidian fever.

(d) *Irregular Quartan Fever.*—A multiple infection may result in an almost continuous fever.

A multiplication of parasites introduced originally in small numbers may convert a simple into a double or a double into a triple quartan fever. On the other hand, weakening of a strain of parasites in a triple infection may reduce it to a double or even a simple quartan type.

3. Symptoms due to Laverania Malariæ

The fevers caused by this parasite are known as æstivo-autumnal or subtertian fevers. The latter name is derived from the fact that the fever is essentially tertian in type although the attacks may be greatly prolonged.

(a) *Simple Subtertian Fever.*—The incubation period is thought to be nine or ten days. Prodromal symptoms like those of simple tertian fever are common. The cold stage may be severe, but is sometimes

absent. The hot stage is associated with severe headache and pains in the back and limbs. Gastro-intestinal disturbances are common, and there may be jaundice. The temperature rises rapidly to 104° or 105° F., and remains high with slight oscillations. There is often a considerable fall just before the crisis (pseudo-crisis). The temperature then reaches its highest point (precritical) and the sweating stage and a rapid fall (crisis) supervene. The temperature generally remains subnormal till the next attack. The duration of the paroxysm is often about twenty-four hours. The duration of the attack in hours deducted from forty-eight will give the length of the interval.

(b) *Double Subtertian Fever.*—This is due to a double infection, leading to a quotidian fever. The attacks are usually comparatively short (six to twelve hours).

(c) *Irregular Subtertian Fevers.*—A multiple infection may lead to a continuous fever, with exacerbations when a numerous brood sporulates. Remittent fevers may arise from prolongation of ordinary paroxysms, so that one attack is not over before another occurs. A remittent type of fever may occur as the result of anticipating attacks. These fevers are often associated with sleeplessness and delirium. In some cases the condition may resemble typhoid and in others there may be hæmorrhages. A scarlatiniform rash may occur.

Bilious remittent fever is a type associated with jaundice, bilious vomiting, and sometimes bilious diarrhœa. The stomach and liver may be very tender. Symptoms may subside, but vomiting, hæmatemesis, hiccough, sometimes epistaxis and other hæmorrhages occur, and the temperature rises greatly and coma and death supervene.

(d) *Pernicious Malaria.*—Specially severe symptoms may arise either from a very severe infection, causing a marked general toxæmia, or from a special accumulation of the parasites in some particular organ, determining severe local symptoms. In either case a high mortality is the result. Several types have been described.

Algid Pernicious Malaria.—This is a very serious condition in which the patient appears in a condition of collapse. The features are sharp, the lips blue, the pulse rapid and of very low pressure, the skin cold and clammy. Coma supervenes, and death generally occurs in a few hours.

Diaphoretic Pernicious Malaria.—In this type the sweating stage may be so marked that the bed and floor may be saturated with perspiration. The patient becomes exhausted, and death from collapse is common.

Hæmorrhagic Pernicious Malaria.—This form is associated with

hæmorrhages, it may be from almost all the mucous membranes, during the paroxysms. A very severe anæmia is rapidly produced. Delirium, convulsions, coma, and death generally result.

Cerebro-Spinal Type of Pernicious Malaria.—Almost any nervous lesion may result from malaria. The parasites may accumulate in the capillaries of the brain and generate toxins, while the combined effect of swollen endothelium, agglutinated red corpuscles, parasites, and pigment may lead to blocking of capillaries or actual thrombosis. Symptoms may be of a general cerebral type or may indicate a more localised lesion. Coma is a common occurrence. It is sometimes recovered from, but may return, the second attack usually being fatal. Delirium may be an early and prominent symptom and is seldom followed by recovery. Symptoms resembling those of tetanus may occur, and convulsions are not uncommon. More localised lesions may lead to hemiplegia, blindness, or aphasia. Symptoms may indicate an intensity of the condition in the medulla, cerebellum, or cord. Malarial meningitis may occur.

Gastro-Intestinal Type of Pernicious Malaria.—Symptoms resembling those of cholera or dysentery are commonly met with. A fair proportion of such cases recover. Acute hæmorrhagic pancreatitis has been found post-mortem in some cases.

Chronic Malaria

This condition may result from infection with any of the parasites, but is usually due to Laverania malariæ.

The symptoms include repeated attacks of slight fever, pigmentation of the skin and mucous membranes, and slight yellow colouration of the skin in many cases.

The urine shows an increased output of urea and urobilin. The liver and spleen are enlarged. There is great lassitude and often severe anæmia. During febrile attacks parasites may be found in the blood. A continuance of this condition leads to *malarial cachexia*, in which there is emaciation and enormous enlargement of the spleen, which is firm and not tender. Traumatic and even spontaneous rupture of the spleen may occur. Parasites are not readily found in the blood unless a febrile attack should occur.

A person who has once had malaria is liable to have occasional attacks months or years after the date of infection.

In *latent malaria* parasites, usually æstivo-autumnal forms, may be

found in the blood although symptoms are absent. The parasites are usually crescents, which, according to Ross and Thomson, persist by constant regeneration but do not live long individually.

Sexual forms do not cause fever.

The Blood in Malaria.—The parasites inhabit the red corpuscles and may be seen in fresh specimens. The movements of the parasites and of their pigment readily attract attention, particularly in tertian fever, the Plasmodium vivax being specially active. The finer structure of the parasite can only be determined in stained specimens. Thin evenly-spread films give the best results, but if a mere rapid diagnosis is required, then the method introduced by Ross may be employed. Many variations in the technique have been suggested.

1. A large drop of blood is spread out on a slide and allowed to dry in air or slightly heated. The film is then covered with an aqueous solution of eosine and stained for fifteen minutes. It is next washed gently and the red corpuscles lose their hæmoglobin. The film is then stained for a few seconds with alkaline methylene blue, washed, dried, and mounted. Or the alkaline methylene blue may be used in very dilute solution, and the stain correspondingly prolonged.

2. Another method is fixation in absolute alcohol, dehæmoglobinisation with 1 per cent. acetic acid, and subsequent staining; or fixation may be carried out with acid alcohol (5 per cent. acetic acid in absolute alcohol).

3. Films may have their hæmoglobin washed out with water and then staining is effected with Leishman's dye.

4. We find that we get excellent results with the least possible trouble by immersing the thick film as soon as it has dried in a very dilute solution of Leishman's stain in tap water. Twenty to thirty drops of the dye in an ounce of water is sufficiently strong. The film may be left in this for an hour or more. The length of time taken in staining depends a good deal on the thickness of the film, and it is well for beginners to control it by occasional microscopic examination under a medium power. When staining is complete the whole film has a transparent blue colour. It is then rinsed gently with water, allowed to dry, and mounted in balsam.

The advantage of these methods is that a much larger quantity of blood can be examined quickly than by the ordinary film method. The staining of the plasmodia is the same, and as nothing is left in the

film except the leucocytes, the plasmodia, and the fibrin threads which hold them in position, the search for parasites is much easier, especially in cases where they are few in number.

Any basic dye will demonstrate the parasites in ordinary films, but the best results are obtained by the use of a Romanowsky dye. We prefer Leishman's method. The nuclear chromatin stains a bright red with the azur contained in the mixture. The characters of the parasites have been described in discussing their life-history and are illustrated in Plate XV.

Thomson[1] has devised a special pipette for the enumeration of the actual number of parasites in a unit of blood, and it may, of course, be used to count other parasites, such as trypanosomes, and also leucocytes. From our experience of it we are conservative enough to prefer the older method of leucocyte counting, but there seems no doubt that in expert hands it is capable of giving accurate results, and it is certainly the best means of enumerating parasites. The pipette, which is made by C. Baker, 244 High Holborn, London, is a capillary tube made of thick glass, graduated in $\frac{1}{8}$ of a c.mm. The blood is drawn directly into the tube, $\frac{1}{8}$ c.mm. is then blown out on a clear glass slide, kept moist by breathing on it, and spread out with a needle into a square 4 mm. $\times$ 4 mm. This film is allowed to dry and then stained as usual. It must be examined with a mechanical stage, an immersion lens, and a square diaphragm in the eye-piece. The counting is done by finding the number of fields from top to bottom of the square, and counting bands across the whole film at, say, the 5th, 10th, and 15th fields from the top. If the number of fields from top to bottom be 30, and the average number of leucocytes in each band be 40, then the total number in the square film is $30 \times 40 = 1200$. The square film represents $\frac{1}{8}$ c.mm., so the number per c.mm. is $8 \times 1200 = 9600$. It is obvious that the accuracy of the result will depend entirely on the even spreading of the film, and that uneven spreading can only be overcome by counting the whole square film. One great advantage of the method is that the specimens can be stored for reference.

The pipette must be cleaned at once with water, alcohol, and ether successively. Blocked pipettes may be cleared by immersing them in a test-tube containing nitric acid, and placing the test-tube in a beaker of water which is alternately boiled and cooled.

The blood in malaria may be profoundly altered.

[1] *Ann. of Trop. Med. and Parasit.*, December 1911. *Med. Press*, 24th April 1912.

Red Corpuscles.—As every sporulation causes destruction of the infected red cells, anæmia is always a feature of malaria. This is usually mild in tertian and quartan, but may be very severe in æstivo-autumnal fever. In tertian fever the infected red cells are enlarged and partially decolourised.

Specimens prepared with Leishman's stain may show fine red points (Schüffner's dots) in some of the infected red cells. These are probably the result of degeneration. In quartan malaria the infected red cells are rather smaller than normal, and exhibit a slightly darker colour. In æstivo-autumnal fever the infected corpuscles may become decolorised, particularly those containing crescents. Some of the corpuscles show Schüffner's dots and others show larger and more irregular areas, which stain red with Leishman's dye. These are known as Maurer's dots. Again, some of the red cells become shrunken, and in fresh specimens show a brassy colour.

In attacks of ordinary severity the anæmia induced by one paroxysm has to a considerable extent been recovered from before another takes place, but even in quartan fever, if long continued, secondary anæmia may result. This may assume the picture of an ordinary secondary anæmia with the characteristic alteration of the leucocytes, or there may be very marked blood changes, not merely due to blood destruction by the parasites and their toxins, but also to damage to the bone-marrow.

The milder changes include poikilocytosis, anisocytosis, a low colour index, and the presence of a few normoblasts. In more severe cases there are in addition polychromasia, punctate basophilia, and megaloblasts and megalocytes, with a colour index tending to be high. Prognosis in such cases is very grave. In another type of anæmia there is little indication of bone-marrow reaction. The red cells are small and misshapen, greatly reduced in number, polychromasia is absent or slight, and nucleated red cells are scanty or absent. Prognosis is also grave, but the course is more prolonged than in the megaloblastic type of anæmia.

Leucocytes.—During the paroxysms there is usually at the very beginning, and lasting for about half an hour, a more or less marked leucocytosis, polymorphonuclear cells being specially increased. This is succeeded by leucopenia, affecting the total numbers of both polymorphs and lymphocytes, which is most marked at the end of the paroxysms and continues in the apyretic intervals. Differential counts during the intervals show an increase of large lymphocytes, particu-

larly of the large mononuclear or large hyaline type. Polymorphs range from 40 to 65, large lymphocytes from 15 to 40, small lymphocytes from 15 to 20 per cent. Eosinophils are usually less than 1 per cent. In some cases the lymphocyte percentage may be even higher—up to 90 per cent.

Arneth's classification shows a drift to the left and a few myelocytes may be seen, especially in the severe cases with megaloblastic anæmia. Many of the large lymphocytes, a few polymorphs, and an occasional eosinophil may be seen containing pigment. Large lymphocytes may show phagocytosis towards the parasites and red cells containing them. It is quite evident that lymphocytes, especially the large forms, are the active agents of defence in malaria. They vary in percentage and total number inversely with the temperature, being low when it is high, and rising at once when it falls.[1]

In the chronic forms there is leucopenia with a high percentage of lymphocytes, especially the larger forms. In the severe æstivo-autumnal forms there may be a considerable increase in the total number of white cells—up to 30,000 or more. This is usually a real lymphocytosis.

Thomson (*l.c.*) asserts that in quiescent or latent malaria, and in cases apparently cured by quinine, the lymphocyte fluctuation is replaced after a certain time—a few days up to a week in mild cases, ten days or longer in severe cases or debilitated persons—by a polymorph fluctuation. This takes the form of a leucocytosis, rising even to 125,000, and often as high as 40,000, which lasts only a few hours or even less, and is markedly periodic in occurrence, being quotidian, tertian, irregular, etc., according to the type of the original fever, and coming on at the same time of day as the original attack. The cause of this phenomenon is uncertain, but must apparently be the persistence of some periodic virus, it may be the sporulation of a very small number of parasites. If this is so, it is certainly remarkable that the sporulation of a large number of parasites should cause a leucopenia, and of a small number a leucocytosis.

Times at which to Examine the Blood for Parasites.—Parasites can be found in the blood during the chill, but from eight to ten hours after the commencement of the tertian rigor they are usually most numerous, and this time has the further advantage that the characteristic leucopenia is usually present. In simple tertian fever most of the plasmodia are now seen as rings. The amœboid forms appear

[1] Thomson, *Ann. of Trop. Med. and Parasit.*, April 1911.

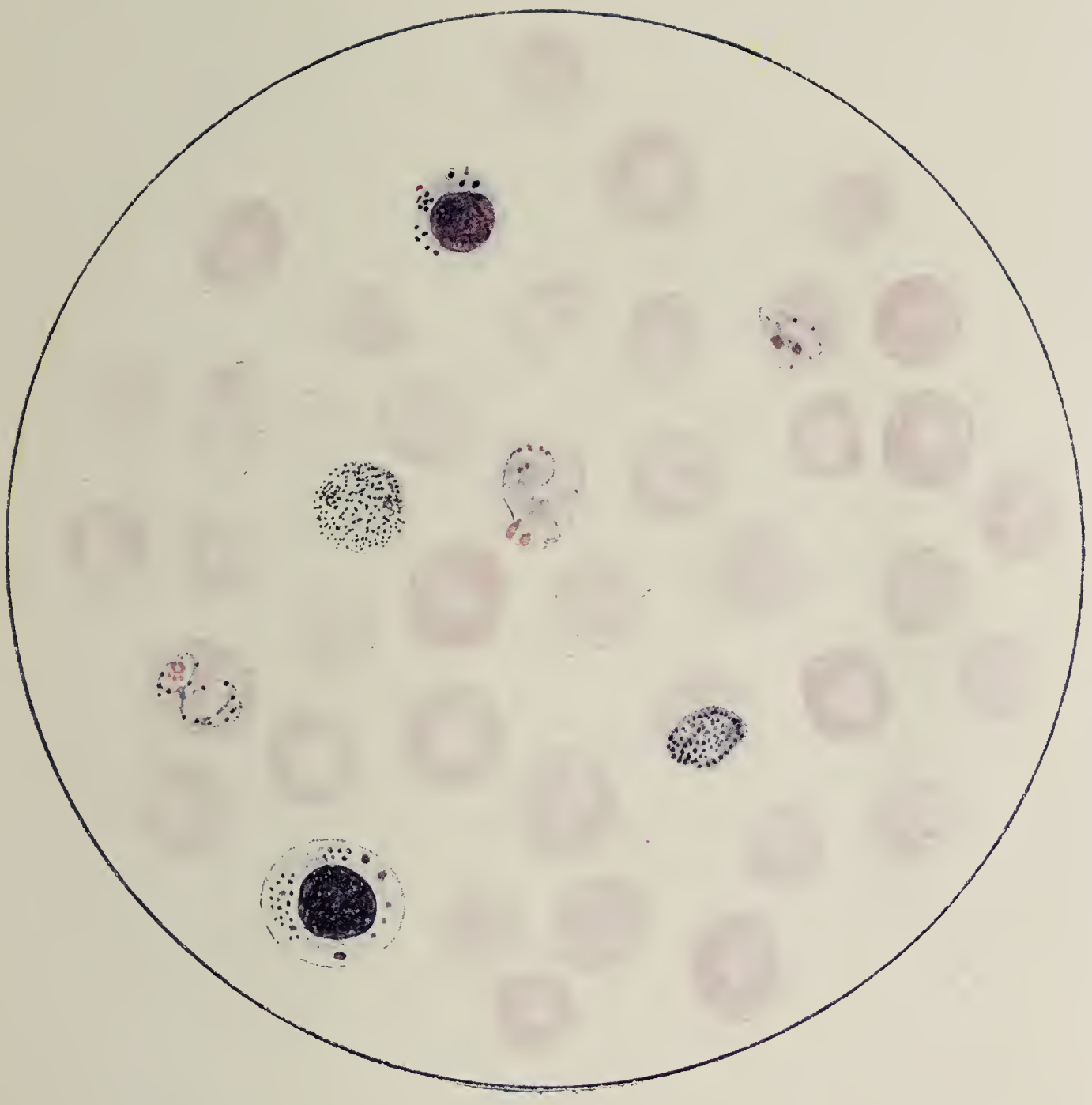


PLATE XVI.—BLOOD FILM FROM CASE OF TERTIAN MALARIA, TAKEN TWENTY-SIX HOURS AFTER THE BEGINNING OF A PAROXYSM (Leishman's Stain).

There are no young forms.
Trophozoites and schizonts are present; large lymphocytes show pigment. In the lower one are also azur granules.

A. G., *fecit.*

from this time onwards to the end of the first twenty-four hours. For the next twelve hours the full-grown parasites are seen, in the form of large spherical bodies containing much pigment, while the form preceding segmentation appears generally about eight hours before the next rigor is due. Rosettes appear about three or four hours before the rigor, are most numerous just before it occurs, and quickly disappear after it.

In cases where there is any doubt about the diagnosis care should be taken not to give quinine until after films have been made, unless the symptoms are so urgent as to make immediate treatment imperative. Even in cases treated with quinine parasites may be found up to eighteen hours after the rigor, but they are usually very scanty.

The appearances of the quartan parasite correspond roughly to those of the tertian, with the necessary lengthening of the time involved. This affects rather the period of growth in the middle of the cycle than the incidence at beginning and end.

In æstivo-autumnal fever the small rings may be found at about the same time as in tertian. The characteristic signet-ring form appears about twenty-four hours after the rigor; thereafter the appearance of parasites varies greatly in different cases. In some the amœboid forms are very scanty or apparently absent, and in cases treated by quinine they often disappear about the third day. In others they are numerous, and may persist for nearly a week. Segmentation occurs in the internal organs, not in the blood. Crescents are generally to be found after the fourth day, sometimes a little later, and may persist for two or three weeks, or longer, even though quinine be given.

The actual number of parasites found in the peripheral blood varies greatly in different cases. Speaking generally, they are more numerous in the severer cases; but it is to be remembered that patients who have been energetically treated with quinine may die of the attack with very few parasites to be found in the blood. Cases of coma and hæmatemesis are specially likely to show this.

Diagnosis.—The typical incidence of the paroxysms in tertian and quartan fever makes the diagnosis easy. In irregular or quotidian fevers the temperature chart does not help. The diagnosis can be made with certainty by microscopic examination, and in any case should always be confirmed by it. Ross considers that fever is not likely to arise unless parasites number at least 1 to every 100,000 red corpuscles, while in a severe case the proportion of infected corpuscles may be 12 per cent.

If a definite febrile attack is due to malaria, there is little reason why the possessor of a microscope who knows how to use it should be unable to find the parasites. In stained films they are readily recognisable, and cannot readily be mistaken for anything else. The novice is more likely to imagine he sees parasites when they are absent than to overlook them when they are present. Dust particles, precipitates of stain, and spots on erythrocytes due to imperfect drying are apt to be mistaken for parasites. If a beginner is in doubt as to whether any given object is a parasite, he should regard it as something else. He is not likely to have a doubt about a genuine find. Pigmented leucocytes may be noticed.

In chronic malaria and malarial cachexia parasites may not be readily found. Splenic puncture might reveal them, but is not without danger. Resistance to quinine does not necessarily exclude malaria.

In difficult cases a close record of the temperature, the splenic enlargement, the differential leucocyte count, the periodic pains, the general aspect of the patient, and the effect of quinine must all be carefully considered. Urriola[1] recommends a careful search of centrifuged urine for malarial pigment.

There is a tendency on the part of persons in this country who have had malaria, and to a certain extent on the part of their medical attendants also, to diagnose as malaria all febrile conditions occurring five, ten, or fifteen years after their return from malarious districts, especially if there be any tendency to rigor or irregular temperature. Mistakes are most likely to occur with deep-seated suppurative conditions, such as prostatic abscess, pyelitis associated with blocking of the ureter, cholecystitis, etc. Practically all of these will show a persistent leucocytosis and a glycogen reaction. But we have seen puerperal septicæmia, typhoid, and pneumonia diagnosed for too long as malaria. In all these cases, apart from history and physical signs, a proper blood examination would have made the condition evident.

Prognosis.—In simple tertian and quartan fevers prognosis is good. In quotidian fever due to tertian or quartan parasites it is more serious. Æstivo-autumnal fever in any form is still more serious, and any form of pernicious malaria is a grave condition. Immigrants to a malarial district suffer more severely than natives. Prognosis is worse in warm than in temperate climates. The disease is more dangerous at the extremes of life. If the disease has existed for some time without treat-

[1] *La Semaine Méd.*, 4th January 1911.

ment it is more serious. Complications, of course, add to its gravity. A very important factor is resistance of the condition to the action of quinine or intolerance of the patient towards that drug.

Treatment.—*Prophylaxis.*—Sanitary and engineering works directed towards the suppression of anophelines have practically banished malaria from various localities.

The chances of infection by mosquitoes may be diminished by suitable arrangement of dwelling-houses, which should be built on a height if possible, and remote from water likely to be a breeding-ground of the insects. Mosquito-proof houses and mosquito curtains are valuable protectives.

The prophylactic administration of quinine should be regularly carried out in malarial districts. Various methods of giving the quinine are employed.

Koch recommends 15 grs. of quinine on two consecutive days every eight or ten days. Castellani and Chalmers give 5 grs. daily and an additional double dose on Sundays. Young children require smaller doses, and euquinine in sweetened milk or chocolate may be employed.

Symptoms of cinchonism may arise, and in that case the drug must be left off for a few days.

Treatment of the Disease.—When an attack begins the patient must go to bed. In the cold stage he should be kept warm, and warm drinks are indicated.

The headache may be relieved by the application of ice or cooling lotions.

The patient's garments should be changed after the sweating stage, and cold or tepid sponging is grateful and may induce sleep.

Constipation should be avoided, and diarrhœa should not be checked unless excessive. In delirious and comatose patients the condition of the bladder must be seen to regularly.

The diet should be light and stimulating. Milk, albumin water, and meat extracts may be given during a paroxysm, and alcoholic stimulants may be indicated. During remissions milk puddings and soups may be allowed. During intermissions the patient may be allowed ordinary meals of plain food.

Medicinal Treatment.—The one drug which has a definitely curative effect is quinine. It acts vigorously on the young forms, less actively on the schizonts, but has much less effect on the gametocytes, particularly

the macrogametocyte of æstivo-autumnal fever. In ordinary simple tertian or quartan attacks a dose of quinine may be administered thrice daily, or the administration may be arranged to forestall the sporulation of the parasites. It may be difficult to get the patient to retain quinine given by the mouth during a paroxysm. In such a case, if the infection be mild, there may be no harm in waiting till the temperature falls before beginning the medication. In severe attacks the condition is too urgent to wait for a favourable opportunity of oral administration, and quinine should be given at once by intramuscular or intravenous injection.

For oral administration the bisulphate and bihydrochloride are much more soluble than the sulphate, and are therefore to be preferred unless the matter of expense is a serious consideration. Euquinine is less bitter than the other forms, but is very insoluble and expensive. Pills, capsules, and tablets may be used with advantage in mild attacks, but care must be taken to see that they are soluble. 5 to 10 grs. thrice daily is an ordinary adult dose. For severe attacks or in cases with gastric derangement intramuscular injections are to be preferred to hypodermic administration. Bihydrochloride may be dissolved in normal saline solution and carefully sterilised, and 15 grs. may be injected at a time.

By far the most convenient method is to purchase the quinine dissolved and sterilised in sealed glass bulbs containing a single dose. Several such preparations are on the market. Ordinary precautions as regards the syringe and patient's skin must, of course, be taken.

In very severe infections the drug should be administered intravenously. The injection should be made slowly, and may, if necessary, be preceded by a cardiac stimulant.

The dose for children should not be too small. A child under a year old can take from $\frac{1}{2}$ to $1\frac{1}{2}$ grs. every four hours. Symptoms of cinchonism may sometimes be diminished or avoided by the exhibition of potassium bromide, or opium.

No other drug has the same efficacy as quinine. Good results have been reported from the application of X-rays to the spleen.[1] Methylene blue, preparations of arsenic, and Donovan's solution may be employed. The two latter are useful in malarial cachexia and anæmia. In chronic malaria and malarial cachexia an important part of the treatment is to get the patient out of the malarial district. A sojourn in the Scottish Highlands might be suggested as an ideal change.

[1] Skinner and Carson, *Brit. Med. Journ.*, 25th February 1911.

Symptomatic Treatment.—Symptoms may arise which call for special treatment on general principles. Extreme algid symptoms require hot applications to the body, especially over the heart.

Cardiac stimulants and oxygen inhalations may be employed. Great benefit may follow saline transfusion into the loose fibrous tissue at the lower part of the axilla.

Hyperpyrexia should be treated with sponging or cold packs. The practitioner should be content with a moderate reduction of temperature, since collapse may follow a rapid reduction. Profuse sweating may call for the administration of atropine and stimulants.

Treatment of Convalescence.—The patient must continue the use of quinine for at least three months. Tonics will be indicated, and iron and arsenic will be called for in anæmia. A change to a cool climate is always desirable when circumstances permit. The patient should lead a careful, regular life for at least a year after return to a temperate climate. Drinking bouts, exposure, over-exertion, excitement, etc., may all bring on a recurrence.

CHAPTER XXXVIII

BLACKWATER FEVER

Definition.—An acute febrile disease characterised by great blood destruction and hæmoglobinuria.

Distribution.—The disease is most prevalent in tropical Africa. It occurs in parts of India and China. Cases have also occurred in South America and the West Indies, and it is met with in Southern Europe.

Etiology.—The etiology of the disease is not known. It has a very close association with malaria, and is very commonly attributed to the malarial parasite. Thus it exists where there is severe malaria and is not found where malaria is absent. Persons attacked have always a history of malaria. Parasites or pigment or both can usually be found in the blood. We once examined a blood flow which had been taken five hours before an attack of blackwater fever. It showed very numerous young tertian malarial parasites. Simpson regards the hæmoglobinæmia as the expression of an overflow from the normal channel of excretion, malarial hæmolysis having reached an exceptional degree.

The difficulty in accepting the purely malarial theory is its infrequency in cases of very severe malaria. Moreover, cases occur in which pigment and parasites are absent in the blood and may not even be found in the spleen or marrow after death.

Another view is that the disease is due to quinine. There is no doubt that quinine can cause hæmolysis and hæmoglobinuria, but it is doubtful if it can do so in healthy persons. Other writers attribute blackwater fever to malaria together with the action of quinine, and yet others postulate a third factor, such as renal disease. The difficulty in accepting such views is the absence of blackwater fever in many localities where malaria and presumably the other conditions are present.

The disease is regarded by Manson and others as a special entity, and a variety of parasites, both animal and vegetable, have been suggested as the causal organism.[1] Immigrants to an endemic area are specially liable to the disease, and lowered vitality from any cause is a predisposing factor.

Brem[2] believes that both pernicious malaria with hæmoglobinuria and blackwater fever (erythrolytic hæmoglobinuria) are due to the action of a hæmolysin produced by the malarial parasite, generally of the æstivo-autumnal type. He has prepared extracts of the parasites which are strongly hæmolytic, and finds that the hæmolysin is thermolabile, and that its action is inhibited by the serum of normal persons. To account for the irregularity of occurrence and infrequency of blackwater in malarial infections he suggests that different strains of parasites may generate hæmolysins varying in quantity or virulence, and that they may also be counteracted by such factors as efficient treatment by quinine, or by a relative immunity from previous infections. Or, further, that an antihæmolysin may be formed, generally during the incubation period of a malarial infection, when gradually increasing doses of the hæmolysin are being liberated. The formation of this antibody may be interfered with by exhaustion or exposure, especially in debilitated persons, and perhaps sometimes by the exhibition of quinine.

Morbid Anatomy.—The blood is liquid. The body is jaundiced. The liver is enlarged, the gall-bladder full. The liver cells contain iron-pigment, and are fatty or even necrosed in small areas. There may be thrombi in the sublobular veins. The intestines are usually congested. The kidneys are enlarged and dark coloured. The tubular epithelium is degenerated, and the tubes contain granular material staining as hæmoglobin. The glomeruli contain granular matter, and there is proliferation of capsular endothelium. It has been suggested that the hæmolysis occurs in the kidneys. The bone-marrow may show gelatinous degeneration.

Symptoms.—There may be prodromal symptoms, including lassitude, loss of appetite, pains, restlessness, and slight jaundice. The attack

[1] Cell inclusions and protozoal-like structures have been described by Leishman, *Journ. of Trop. Med.*, 16th December 1912 and 1st January 1913 ; Coles, *Lancet*, 3rd May 1913 ; and Low and Wenyon, *Journ. of Trop. Med.*, 2nd June 1913.

[2] *Arch. of Intern. Med.*, 1912.

is ushered in by a feeling of chilliness and shivering. The temperature rises to 103° or 104° F. There is headache, pain in the back and limbs, and great weakness. There is nausea and bilious vomiting, thirst, and constipation. Occasionally large quantities of blood are passed by the bowel. The liver and spleen are enlarged and tender. The pulse is feeble and rapid. The skin is hot and dry, and rapidly assumes a yellow colour. The conjunctivæ are yellow. The urine may appear normal at first, but soon becomes dark in colour. Occasionally the dark urine is the first symptom noticed. The actual colour may be yellowish-brown, red, or black. Diluted specimens give the spectrum of oxyhæmoglobin, sometimes of methæmoglobin after standing. The reaction is faintly alkaline. The specific gravity is often low. A sediment of broken-down red corpuscles and blood-pigment appears after the urine has stood. The presence of urobilin can be made out by acidulating the urine with acetic acid, extracting the pigment with amylic alcohol, and examining with the spectroscope. Bile pigments are sometimes present, and there is usually albumin and globulin. There may be symptoms of uræmia. Coma and delirium are not uncommon. After a few hours symptoms may lessen. Perspiration begins, the temperature falls, the urine clears, and recovery may take place. On the other hand hyperpyrexia, coma, and death may occur. Even after a remission the temperature usually rises again with a return of symptoms, and a succession of such relapses may cause death by exhaustion. After the attack the patient is very weak. Convalescence is prolonged and kidney symptoms are apt to arise.

The Blood Changes.—The blood is thin and watery. There is hæmoglobinæmia and cholæmia. The red cells are greatly reduced in number. The hæmoglobin is reduced but the coloured plasma leads to a fairly high colour index. Many of the red corpuscles are represented by mere shadows or fragments. At a later stage polychromasia and the presence of nucleated red cells may be found. Malarial parasites may be seen. During the fever there is leucocytosis due to increased polymorphs. During remissions there is leucopenia, with an increase of large mononuclear cells. Malarial pigment may be noticed.

Prognosis.—The prognosis varies in different epidemics and in different districts. Mortality ranges from 4 to 50 per cent.

Treatment.—*Prophylaxis.*—In the present state of our knowledge prophylactic measures directed against malaria probably apply to this disease. A person who has once had blackwater fever should not remain in the tropics. This rule has been broken with apparent impunity, but the risks of disregarding it are very great.

Treatment of the Disease.—The patient should be in bed. The diet should be liquid. Milk, whey, albumin water, gruel, etc., should be the main items. Meat extracts are better avoided.

An attempt should be made to flush the kidneys. Large quantities of soda water, barley water, etc., should be taken by the mouth whenever possible. If gastric irritability does not permit of this, saline enemata or saline transfusion into subcutaneous tissue may be carried out. Cardiac stimulants are indicated. Chlorides, especially calcium chloride, have been recommended. If malaria parasites are present quinine should be administered in the form of bihydrochloride. The sulphate should be avoided because of its hæmolytic action.

Uræmic symptoms may be treated on the usual lines, and a variety of symptoms may call for special attention.

Convalescence requires general tonic treatment and special treatment for anæmia. The diet should be restricted in view of probable damage to the kidney. As soon as possible the patient should remove to a temperate climate.

CHAPTER XXXIX

KALA-AZAR

Definition.—A disease caused by a protozoal organism in the spleen and other organs and occasionally in the blood, characterised by long-continued fever, anæmia and debility, and enlargement of the liver and spleen, usually resulting in death.

Distribution.—The disease is endemic in Assam and to a less extent in Lower Bengal. Large epidemics are frequent. Cases have occurred in practically all parts of India, in the Soudan, and have been reported in other parts of the world, but in some instances it is uncertain whether the disease has been endemic or imported.

Etiology.—There is now little doubt that the infecting agent is the Eastern bed-bug, *Cimex rotundatus*, whose bite introduces a parasite, the *Leishman-Donovan body*.

Patton has recently followed out the whole cycle of development in bugs, both Cimex rotundatus and C. lectularius (the European bed-bug), by feeding them on a case which contained the parasites in the circulating blood. He was able to trace the parasite from its unchanged state in leucocytes, through the flagellate stage, to the rounding up in the post-flagellate form. If bugs containing developing forms are fed on another case (a monkey suffering from kala-azar was used), the flagellating forms are destroyed within twenty-four hours, but if they are not fed again, development goes on and is completed in C. rotundatus in from ten to twelve days after the single feed. This interesting fact probably prevents many bugs from becoming infective, and prevents the spread of the disease outside its endemic areas. Patton found also that development took place as easily in C. lectularius as in C. rotundatus, and in a rather shorter time—from seven to ten days—and he considers that this is the probable explanation of the infantile kala-azar (*q.v.*). Seen in fresh unstained preparations the parasites appear as refractile colourless bodies of indefinite outline, somewhat resembling blood-plates. Stained by Leishman's method they appear as

sharply-defined round or oval bodies, measuring from $2{\cdot}5 \times 1{\cdot}5$ to $3{\cdot}5 \times 2\ \mu$. The body of the parasite stains a faint blue colour. It contains two masses of chromatin, one large and round, the nucleus, the other smaller, often rod-shaped and more deeply stained, the blepharoplast. These masses often lie at opposite ends of the smaller diameter of the parasite, with the long axis of the smaller at right angles to that of the larger.

The parasites can be cultivated outside the body. They develop in citrated blood rendered acid by the addition of citric acid. The optimum temperature for their cultivation is 20 to 22° C. In cultures flagellate forms develop, and this fact led to the suggestion that the organism was a phase in the life-history of a trypanosome. No undulating membrane, however, develops, and the flagellum is at the blunt posterior end of the parasite next the micronucleus. It is probably a herpetomonas.



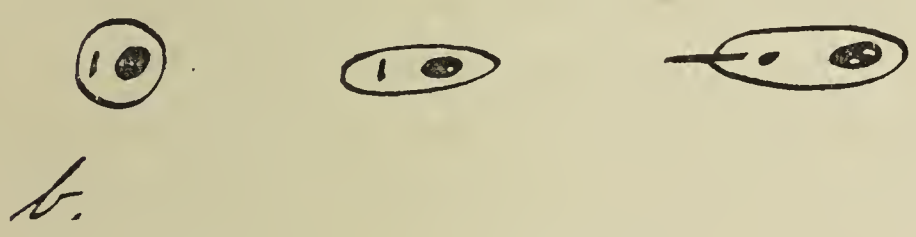


FIG. 28.

a. Stages in the development of trypanosome. *b*. Stages in the development of the Leishman body.

Morbid Anatomy.—There is great enlargement of the spleen and liver, inflammation of the large intestine, and often effusion of serous fluid and œdema. The splenic enlargement is massive. Perisplenitis is usually absent. The spleen substance is firm but friable. On section the surface is dark red. On microscopic examination there is great dilatation of the sinuses and atrophy of the Malpighian bodies. Scattered throughout the pulp are generally enormous numbers of the parasites. They are found chiefly in the endothelial cells but also in the large lymphocytes and in smaller numbers in the polymorphs. They are not found in the Malpighian corpuscles.

The enlargement of the liver is not so great as that of the spleen. The organ is firm but friable. There is usually a good deal of fatty change and a considerable deposition of iron-containing pigment. There

is some proliferation of endothelial cells. Parasites are numerous in endothelial cells and in free mononuclear cells, but do not occur in the liver cells,

The large intestine is often inflamed and thickened and may be ulcerated. The small intestine may show the same changes in a minor degree.

A few parasites may be found in the endothelium of capillaries.

In uncomplicated cases the other organs are usually healthy. Parasites are numerous in the bone-marrow, chiefly in the large lymphocytes, but there are also a few in the myelocytes. Parasites are also found in small numbers in the capillaries of most of the other organs and in the lymph glands, particularly those of the mesentery.

Symptoms.—The incubation period is not known, but symptoms have developed in patients months after they had left an infected area. The symptoms of the disease often develop in three stages—the initial fever, secondary fever, and cachexia. These stages are not always sharply defined.

First Stage.—Sometimes the onset of the disease is very insidious, but perhaps more frequently it begins with rigors or chills which may recur daily. The fever is usually remittent, but later becomes intermittent. In most cases the rise of temperature takes place in the evening, but in some cases there may be two or even three daily exacerbations of fever. After some days the spleen becomes enlarged and tender and the liver shows the same changes in a less degree. Anæmia and wasting are early features. The skin may become darker, and headache is sometimes complained of. The appetite as a rule remains good.

This stage may last for from ten to sixty days, commonly about a month.

Second Stage.—There may now be a short interval, during which the patient appears to recover, but this feature is often absent. The patient then shows a low fever of very varying type for weeks or months or even a year. The liver and spleen continue to enlarge, the latter enormously.

Third Stage.—There is now very marked cachexia, with great emaciation and weakness. The temperature is often subnormal. The appetite is ravenous in many cases. Diarrhœa is generally a prominent symptom, and is perhaps the most frequent cause of death. The end is often brought about by asthenia or by a complication such as pneumonia or cancrum oris.

The total duration varies from a few months to two years and is usually rather over a year. Atypical cases are fairly common.

Blood Changes.—Anæmia is a constant feature. The number of red and white corpuscles may be said to diminish progressively throughout the disease. The red cells are very commonly found to number 3,000,000 per c.mm. The hæmoglobin is rather more than correspondingly diminished. The usual features of secondary anæmia are present.

White Cells.—These are diminished, and some remarkably low counts have been recorded. Reduction to 3000 is common, but the number may fall as low as 500 per c.mm.

The decrease chiefly affects the polymorphs, so that there is a considerable relative lymphocytosis, especially of the large variety. Polymorphs are often reduced to 40 or 50 per cent. Small lymphocytes comprise 20 to 30 and large lymphocytes 15 to 20.

Rogers states that the ratio of white to red cells falls as low as 1 to 1000 in all uncomplicated progressive cases, and holds that a reduction of the ratio to 1 to 1500 is diagnostic of kala-azar from other Indian fevers.

The parasite occurs only sparingly in the blood, and is said to be found more easily when the temperature is high. It is contained in the large lymphocytes and polymorphonuclear cells.

In order to find the parasite a large number of leucocytes must be brought under review, either by examining the edges of thick films, or by making films from the leucocyte layer of centrifuged blood. It is the exception rather than the rule to find the parasite in peripheral blood.

Malaria parasites or pigment may be present as a complication.

Diagnosis.—At the onset of the disease the diagnosis is attended with very great difficulty. It may present a close resemblance to typhoid or malaria. In one case which was under our care the difficulty of diagnosis from typhoid in the early stage was increased by the presence of a positive Widal reaction. Even in the later stages it may be difficult to differentiate the disease from malarial cachexia, and the two conditions may co-exist.

The only certain diagnostic is the demonstration of the parasite, and it is often impossible to find it in the peripheral blood. It is, however, readily obtained by puncture of the liver or spleen. There is considerable risk of even fatal hæmorrhage in the case of the latter procedure

in kala-azar, and liver puncture is to be preferred. This measure is carried out by means of a sterile syringe, which must be dry, as moisture may disintegrate the parasites. The skin is sterilised and the needle is plunged deeply into the liver with a slight rotatory movement. The syringe should follow the respiratory movements of the liver. After about a minute gentle aspiration is effected. It is not desirable to obtain much blood, as it only dilutes the lymph containing the parasites. The fluid thus obtained is spread into a series of thin films, which may be stained by Leishman's method. The number of parasites so obtained varies very greatly. They may be free or contained in cells or embedded in a matrix. This matrix is not seen in smears made from organs after death and is not seen in sections. It is probably due to the disintegration of phagocytic cells which have taken up the parasites.

Prognosis.—Authentic cases of recovery are on record, but the mortality is very high, probably not less than 96 to 98 per cent.

Treatment.—Prophylactic treatment appears to consist in the avoidance of too close an acquaintanceship with *Cimex rotundatus*. Price and Rogers give an interesting account of the effect of a removal of Coolie lines from an infected area. The new huts were only 400 yards from those severely infected, yet no case had occurred in the new lines during sixteen years. The treatment of the disease is unsatisfactory. Cures have followed the use of atoxyl. Quinine in large doses has been said to do good. Arsenic, salicylates, and drugs calculated to increase the number of leucocytes have all been tried. Symptomatic treatment is of course called for, and in the case of Europeans removal to a temperate climate may do good and will certainly add to the patient's comfort.

Literature

For the history of the discovery of the parasite and its characters, see Rogers, *Proc. Roy. Soc.*, 1906, 284, and *Brit. Med. Journ.*, 23rd February, 2nd and 9th March 1907 ; Price and Rogers, *Brit. Med. Journ.*, 7th February 1914.

Infantile Kala-Azar

This disease, met with in Southern Italy, Sicily, Malta, and North Africa, appears to be identical with Indian kala-azar.

Etiology.—The disease is due to the parasite Leishmania infantum

(Nicolle), which is similar to the Leishman-Donovan body. It has been inoculated into monkeys and dogs. Nicolle regards the dog as a reservoir of the virus, and considers that its ectoparasites, such as fleas, are the transmitting agents to human subjects, but Patton's recent observations on bugs (p. 350) may cause this view to be modified.

Symptoms.—The disease cannot be distinguished from ordinary kala-azar, except that it usually affects children from one to six years of age. It generally begins with irregular attacks of fever. There is progressive anæmia, and polymorphs are diminished. The liver and spleen are enlarged, and there is great emaciation and sometimes cutaneous hæmorrhages. Duration is from a few months to several years. The outcome is usually fatal.

Diagnosis.—The diagnosis is made by finding the parasite by liver or splenic puncture. Pianese recommends puncture of the superior end of the tibia and examination of the marrow for parasites. Cretien[1] has found the parasite in mucous flakes in the fæces.

Treatment.—Treatment is unsatisfactory, and is on the same lines as that of Indian kala-azar.

[1] *Brit. Med. Journ.*, 28th January 1911.

CHAPTER XL

TRYPANOSOMIASIS

THE occurrence of trypanosomes in the blood of fish and amphibians has been known for over sixty years, and numerous varieties have been described in these animals as well as in reptiles, birds, and some invertebrates. It is only within recent years that their importance in mammalia has been recognised, and in 1901 they were discovered to be pathogenic to man.

Characters.—Trypanosomes are fusiform in shape and have a longitudinal membrane along the side. The thickened border of this membrane ends posteriorly in a small mass of chromatin, the blepharoplast or centrosome, and is prolonged anteriorly into a free flagellum. The nucleus is generally anterior. The organisms are actively motile. Reproduction takes place by simple division. The parasites divide longitudinally and unequally. Whether previous conjugation occurs is not determined with certainty.

Trypanosomes can be cultivated on artificial media. Sterile defibrinated blood is added to ordinary nutrient agar after cooling to 50° C. Unaltered hæmoglobin seems to be essential. Abundance of oxygen and moisture are necessary. Cultures at room temperature retain their vitality for months. In the incubator growth is more rapid, reaching a maximum in eight to twelve days, death occurring in three weeks.

The following varieties are of special importance :—

T. Lewisi.—This parasite infects rats in all parts of the world. In London 25 per cent. were found to be affected, in Bordeaux 100 per cent. The adult is 27 to 28 μ in length including the flagellum, 1·5 to 2 μ wide. The parasite appears to be harmless in adults but may cause fatal disease in young rats. Its invertebrate host is the flea, but it can also live in the louse and bed-bug.

T. Cuniculi.—This parasite has been found in the blood of wild and tame rabbits. It is morphologically identical with T. Lewisi, but rats are refractory to inoculation with this form.

T. Brucei.—This parasite causes nagana, the "fly-disease" of South Africa. It also occurs in Uganda. The disease is rapidly fatal in horses, and produces a more chronic disease in cattle, sheep, and goats. It causes death in rats in from three to five days, and can be inoculated into practically all the laboratory animals. It has a shorter flagellum and is less motile than T. Lewisi. It varies considerably in length.

T. Evansi.—This trypanosome occurs in India, North America, and Australia. It gives rise to the disease known in India as "surra." It is fatal chiefly to horses but also affects cattle. Length is 25 to 35 μ, and the flagellum is very long.

T. Equiperdum.—The disease caused by this organism is "dourine," which affects horses. It occurs in continental Europe, the East, and the United States. T. Equiperdum is 25 to 28 μ in length, protoplasm is very feebly coloured, and granules are absent. The disease is usually spread by coitus, rarely by biting flies.

T. Equinum causes the "mal-de-Caderas" of South America. It is fatal to horses.

T. Theileri.—This trypanosome infects cattle in the Transvaal. There are large forms up to 70 μ and smaller from 25 to 30 μ in length.

T. Pecorum causes disease in horses and cattle, and is widely distributed in Africa. It is pathogenic to most laboratory animals but not to guinea-pigs.

T. Vivax.—This easily recognisable species gives rise to a fatal disease of cattle in Uganda. The carrier is probably Glossina palpalis.

T. Nanum is a small trypanosome, pathogenic to cattle.

Human Trypanosomiasis—*A.* Sleeping Sickness

A disease caused by the presence in the blood and cerebro-spinal fluid of T. Gambiense, characterised by fever, anæmia, enlargement of lymphatic glands and spleen, and cerebral symptoms, and terminating fatally.

Distribution.—The disease is limited to persons who have resided in South and Tropical Africa. It is specially prevalent throughout the Congo, and within recent years has appeared in the neighbourhood of Victoria Nyanza.

Etiology.—The disease is caused by the bite of a tsetse-fly. The chief carrier is Glossina palpalis, but G. morsitans and possibly other varieties of Glossina may also be vectors. The fly, in some way not understood, infects its victim with T. Gambiense. In some cases there is direct transmission, the fly feeding on an infected animal and immediately afterwards feeding on another susceptible animal. The power of transmission is soon lost, but a certain proportion of flies again become infective twenty-eight days after they have fed on an infected animal. They remain infective for at least ninety-six days. From the eighth to the forty-fourth day after an infective feed a developing form of trypanosome can be found in the gut of the fly. The renewed infectivity of the fly seems to be coincident with an invasion of its salivary glands by trypanosomes.

Morbid Anatomy.—Little is known of the pathological changes in the early stages of the disease in man. In lower animals the chief conditions are congestion of viscera, enlargement of lymph glands and spleen, and sometimes congestion of the brain and cord.

In sleeping sickness there is accumulation of round cells in the perivascular spaces of the capillaries of the brain and spinal cord. The lymph glands are often hæmorrhagic and contain pigment. The spleen is also pigmented. The bone-marrow commonly shows gelatinous degeneration. Evidence of secondary bacterial infection of the brain is often found.

T. Gambiense measures 17 to 25 μ including the flagellum, which averages 6 or 7 μ. Its breadth is 1·5 to 2 μ. The protoplasm contains chromatic granules—chromatophores.

Symptoms.—The incubation period in monkeys is about fourteen days. The onset in man is associated with fever, often of a very irregular type. Some of the lymphatic glands, particularly those at the back of the neck, are slightly enlarged and tender. In Europeans there is usually a rash of very evanescent character, generally taking the form of erythematous rings. They are chiefly to be seen on the abdomen and chest. There is progressive weakness and loss of flesh. There may be muscular tremors and the muscles become tender. The heart is rapid and excitable. The appetite often remains good. After some weeks or months the fever may subside, the patient feels better, and trypanosomes diminish in the peripheral blood, and indeed their presence may only be discovered by inoculating 2 c.c. or more of the

blood into monkeys. This stage may last for some years. Sooner or later the terminal cerebral symptoms make their appearance. The first indication of their onset may be a series of epileptiform convulsions, or a rapidly fatal coma may supervene. The usual course, however, is the onset of an overpowering lethargy. The patient is always drowsy, and may fall asleep during meals or any active occupation. There is mental irritability and incapacity. There is progressive weakness and emaciation even when the patient is regularly fed. Sometimes diarrhœa is a prominent terminal symptom, but death usually follows a more or less prolonged period of coma.

The Blood.—Anæmia is an early symptom, and as the disease advances it may become extreme. Red cell counts of little over a million per cubic millimetre have often been noted. White cells show little disturbance in actual number but their proportions are altered. There is usually an increase of lymphocytes, particularly the large mononuclear variety. Polymorphs are correspondingly diminished. Eosinophils are increased, in some cases even to the extent of 25 per cent. A slight increase of basophils has once or twice been noted.

Diagnosis.—The disease is only diagnosed with certainty by the finding of trypanosomes either directly or by inoculation. In the early stage the parasites may be found with comparative ease in the peripheral blood. Greater certainty of finding the trypanosomes may be attained by withdrawing a few cubic centimetres of blood, mixing them with an equal quantity of 1 per cent. sodium citrate solution, and centrifuging. The trypanosomes are to be sought in the leucocyte layer. Aspiration of fluid from one of the enlarged glands will often reveal the presence of parasites. In the later stage the parasites are to be found in the cerebro-spinal fluid. Some of the fluid is withdrawn by lumbar puncture and centrifuged. In some cases the parasites are never numerous, and a negative diagnosis can only be made after inoculation experiments have failed.

The trypanosomes are readily seen in fresh blood owing to their mobility. They are stained by Leishman's method.

Treatment.—In the case of a disease whose mortality is probably not less than 100 per cent. it is of special importance that preventive measures should be adopted. The prophylaxis of trypanosome disease,

however, opens up very large questions of administration rather than of personal régime, and we must refer readers to works on tropical medicine for their discussion. In the case of the individual the prophylaxis of trypanosomiasis resolves itself into the avoidance of a bite from a tsetse-fly. The treatment of the disease is unsatisfactory. Preparations of arsenic appear to do some good. Atoxyl and its congeners have been largely used, but large doses may cause blindness, and a prolonged course seems to lead to the acquisition of immunity on the part of the trypanosomes. A combined treatment by atoxyl and antimony or mercury seems to be of some benefit. Atoxyl may be given intramuscularly in doses of ten grains on two consecutive days at intervals of fourteen days for a period of two months. In the intervals dilute solutions of antimony or mercury may be employed. Salvarsan does not appear to do good.

B. Rhodesian Trypanosomiasis

In 1910 Stephens and Fantham [1] described a case of sleeping sickness in a patient who had contracted the disease in Rhodesia, where G. palpalis is not found. The carrier is G. morsitans, which, unfortunately, is distributed over a wide range of country, and is not limited to the neighbourhood of watercourses, as is G. palpalis. The trypanosome, *T. Rhodesiense*, shows no very essential difference from T. Gambiense, but its nucleus is often situated posteriorly near the blepharoplast, and its anterior end is longer in many instances. T. Rhodesiense shows a greater virulence than T. Gambiense when inoculated into animals. The course in man is more rapid, and the condition is not amenable to any treatment.

C. South American Trypanosomiasis

In 1909 Chagas found a trypanosome in the blood of a child in Brazil. The trypanosome is *T. cruzi*, and is capable of being transmitted by a bug, *Conorhinus megistus*, to man and domestic animals. Blacklock has shown that T. cruzi is also capable of living and multiplying in *Cimex lectularius*. The parasites found in the bed-bug are infective on inoculation as early as twenty-one hours and as late as seventy-seven days after the infecting feed. Many different forms of the parasite occur in the bug, but it is not known which one causes

[1] *Proc. Roy. Soc.*, B. 83, 1910, 28.

infection in the vertebrate host. Blacklock found that transmission to healthy animals by feeding infected bed-bugs on them was of very rare occurrence, but Chagas has successfully inoculated marmosets, dogs, cats, guinea-pigs, and rabbits by allowing the infected Conorhinus to bite them. He has also cultivated the trypanosome on blood-agar. Three forms are found in the blood, one with a large nucleus and a terminal micronucleus, a second narrower with oval nucleus, and a third with a long nucleus.

Symptoms.—There are attacks of remittent and intermittent fever, œdema, glandular enlargements, splenic hypertrophy, anæmia, and wasting. In children there is maldevelopment. The trypanosomes occur in the blood only during pyrexia. Some cases terminate fatally, the majority pass into a condition of chronic illness.

Literature

Chagas, *Arch. f. Schiffs- u. Tropen-Hygiene*, 1909 ; *Brazil Medico.*, 22nd April 1909 ; *Bulletin de la Soc. de Path. Exotique*, 1909 ; Blacklock, *Brit. Med. Journ.*, 25th April 1914.

CHAPTER XLI

DISEASES DUE TO SPIROCHÆTES IN THE BLOOD

SEVERAL species of pathogenic spirochætes are known. These include Spirochæta Obermeieri, the cause of relapsing fever; S. Duttoni, the cause of African tick fever; S. Theileri, which affects cattle in South Africa; S. Gallinarum, affecting fowls in Brazil and the Soudan; S. Granulosa, found in Soudanese fowls; S. Anserina, the cause of disease in geese; and the spirochæta pallida of syphilis.

These organisms all cause fever, and are found in the peripheral blood. It has been demonstrated that certain of them are conveyed by the bite of ticks. S. Duttoni is transmitted by Ornithodorus moubata, S. Theileri by Boophilus decoloratus, and S. Gallinarum by Argus persicus.

There seems to be a definite though slight distinction between the European relapsing fever due to S. Obermeieri and African tick fever due to S. Duttoni. Owing to still slighter differences it has been suggested that there is a North African type due to S. Berbera, an American type of relapsing fever due to S. Novyi, and an Asiatic type due to S. Carteri.

RELAPSING FEVER

A disease characterised by the occurrence of febrile paroxysms associated with the presence of spirochætes (spirilla) in the blood.

Distribution.—The disease was formerly common in the British Islands, particularly in Ireland. Its association with destitution gave it the name "famine fever." Recent epidemics have occurred in Austria and Russia. In epidemic form the disease is most common in India, particularly the Bombay Presidency, but outbreaks have occurred in recent years in China, Northern Africa, South America, and the West Indies.

Etiology.—The disease is due to the presence of Spirochæta Obermeieri in the blood. The parasite is a delicate thread-like organism,

measuring 15 to 40 μ in length, 0·25 μ in breadth at its widest part. It exhibits a number of spirals, very commonly eight. The extent of the bending varies greatly. The organism exhibits extraordinary motility, being capable of progression backwards and forwards as well as of performing lateral and rotatory movements.

When faintly stained with a Romanowsky method the spirilla appear blue, when more deeply stained they are red. They are also stained by carbol-fuchsin or gentian violet. They are decolourised by Gram's method. No details of structure can be detected beyond the existence of tapering pointed ends and slight inequality of staining intensity, the central portion staining least. Attempts to cultivate the spirilla have failed. It is not known how the organisms find entrance to the body.

Local infectivity is very marked, but the disease seldom spreads widely. Attendants on the sick are especially liable to attack, and instances of successive inhabitants of a house or room being infected are common.

The fact that other spirilla are conveyed by ticks has led to inquiry in this direction. The spirillum has been found in bugs, and is known to live in them for several days. Infection has been conveyed to monkeys by injecting the fluids of infected bugs crushed immediately after feeding, but bugs crushed forty-eight hours after feeding failed to convey infection.

In an epidemic in India Mackie regarded Pediculus vestimentorum as the infecting agent, and he found spirilla in the secretion expressed from the mouths of pediculi from infected persons.

The blood of a patient in the apyrexial period, during which spirilla are not found, is still infective to monkeys. This has suggested the existence of spores, but these have not been demonstrated although "infective granules" have been described. These granules may be demonstrated by the dark-ground method or by vital staining. Blood containing spirilla causes relapsing fever when injected in man, monkeys, rats, and mice.

Morbid Anatomy.—The general picture is that of severe septicæmia. There are subserous hæmorrhages, and enlargement of the liver and spleen, and catarrh of the mucous membranes. The splenic capsule is distended and smooth, the pulp is firm and the Malpighian bodies are enlarged, and there is vascular engorgement. Spirilla may be found free and in polymorphonuclear cells, and are frequently numerous.

The liver shows cloudy swelling. Patches of catarrhal or fibrinous pneumonia are common.

Symptoms.—The incubation period varies from twelve hours to eight days. It is usually two to five days. The initial symptoms are malaise, followed by chills and rigors. There is headache, pain in the back and limbs. The temperature rises to 104° or 105° F., the pulse becomes rapid. Vomiting sets in, and hæmatemesis and jaundice may occur. The patient is sleepless and wretched. These symptoms persist till the third, fifth, or more usually the seventh day, when they suddenly terminate by crisis. The patient, apart from some exhaustion, now feels well, but after seven days there is a relapse, followed by a train of symptoms similar to the first but often of shorter duration. The second attack usually terminates on the fifth day, and is generally followed by complete recovery. Occasionally there is no relapse and on the other hand there may be as many as five. There is very profuse sweating at the times of crisis. The common complications are pneumonia and severe diarrhœa. Less frequently there may be hæmorrhages, inflammation of lymphatic glands, eye and ear, and synovial membranes.

The Blood.—There is a moderate degree of anæmia after the paroxysm. During the paroxysm there is a considerable increase of polymorphonuclear leucocytes and lymphocytes, and spirilla may be found in the peripheral blood. The parasites are much more numerous after the second day of the paroxysm than at the beginning. They are for the most part free and actively motile, but large numbers are often seen in the polymorphonuclear leucocytes. The numbers vary very greatly in different cases, and appear to be very unevenly distributed in the blood. Sometimes they are abundant enough to keep the whole microscopic field in motion, at other times prolonged search may fail to reveal them. They are rarely to be found for two or three days after a paroxysm is over.

Diagnosis.—In the early stages a definite diagnosis may be impossible unless the parasite is found. In the great majority of cases a blood examination will make the diagnosis clear.

Löwenthal has shown that the blood during the afebrile stage will stop the movements of spirilla in blood from a case during a paroxysm when they are incubated together for half an hour.

Prognosis.—In uncomplicated cases prognosis is good. In the British epidemics the mortality was 4 per cent., but it seems somewhat higher in India. Death occurs usually during the height of the initial paroxysm, and is generally due to heart failure. A few cases collapse after the crisis. The disease is more unfavourable at the extremes of age. Pregnant women abort but usually recover. Pneumonia and severe jaundice are generally fatal, and a few cases die from cerebral hæmorrhage.

Treatment.—Prophylactic treatment consists of isolation of the sick from the healthy, and great care must be exercised to avoid the possibility of transmission of the disease by vermin. There is no specific treatment of the disease. Quinine is useless. Possibly the serum of immunised animals might do good. The general treatment must be along lines appropriate for the management of any severe febrile affection. During the apyrexial period the patient should be fed up to the limits of his digestive powers and carefully watched.

Tick Fever

A disease characterised by febrile paroxysms resembling those of relapsing fever, associated with the presence of *Spirochæte Duttoni* in the blood and caused by the bite of an insect.

Distribution.—The disease occurs throughout the greater part of tropical Africa, in Asia, Egypt, and Algeria.

Etiology.—The disease may be caused by the bite of the horse tick, *Ornithodorus moubata*, and by the Persian poison bug, *Argas persicus*. It is probable that infection may also be conveyed by lice and fleas. The bite gives entrance to a spirochæte, *S. Duttoni*. The parasite is identical morphologically with S. Obermeieri, but each of the two forms confers immunity against itself but not against the other. Inoculation of S. Duttoni into monkeys leads to a much more severe disease than S. Obermeieri. S. Duttoni can be cultivated outside the body in special media, such as broth containing mouse blood and yolk of egg.

Ticks may transmit infection from animals which they have bitten during the afebrile stage. Leishman[1] has found that ticks may be

[1] *Lancet*, 1st January 1910.

infective although no spirochætes can be found in their tissues, nor were spirochætes to be found in the eggs or nymphs although the latter gave rise to infective young ticks. Spirochætes ingested by ticks disappear by the tenth day, but their chromatin core breaks up into coccoid granules, which may be found free in the gut in great numbers. Inoculation of emulsions of these granules was infective to mice, especially if the tick from which they were derived had been kept for a day or two at 34° to 37° C. before dissection. Ticks containing the granules develop young spirochætes when kept for a week or ten days at 34° C. The young spirochæte probably passes into the wound made by the tick-bite from the secretion of its Malpighian tubes or coxal glands.

Symptoms.—The symptoms are identical with those of relapsing fever, except that the usual duration of the paroxysm is four days and relapses are more frequent.

CHAPTER XLII

FILARIASIS

A CONSIDERABLE number of filariæ are parasitic in man but only a few are pathogenic. The embryos of *F. Bancrofti*, *F. loa*, *F. perstans*, and *F. demarquayi* are found in the blood. *Filaria medinensis*, the guinea-worm, causes dracontiasis. *Filaria volvulus* is found in lymphatic vessels and gives rise to cystic tumours.

FILARIASIS DUE TO FILARIA BANCROFTI (FILARIA SANGUINIS HOMINIS OR FILARIA NOCTURNA)

Filaria Bancrofti causes disease of lymphatic vessels and glands, chylous extravasations, orchitis, and elephantiasis.

Distribution. — Filariasis is widely distributed throughout Asia, Australasia, America, and Africa. In Europe it is said to exist near Barcelona and in Turkey. The endemic areas are curiously circumscribed for some reason not yet understood.

Etiology.—The condition is caused by the introduction into the body of filaria by means of a mosquito bite. Many different species of mosquito are capable of carrying the disease. *Culex fatigans* is the common infecting agent in the West Indies, *Myzomia Rossii* in India, *Panoplites Africanus* in Central Africa, and *Pyretophorus costalis* and *Stegomyia fasciata* in Nigeria.

The filaria develops in the thoracic muscles of the mosquito and passes to the labium. When the mosquito bites, the filaria works its way though Dutton's membrane on to the skin. There it may find its own way through the skin or it may pass through the puncture made by the mosquito. No more is known of the filaria till its adult condition is reached. Adult males and females are found lying together in lymphatic vessels. Females usually preponderate. The females produce the embryos or microfilariæ, which pass through the thoracic

duct into the blood-stream. When these microfilariæ are ingested by the mosquito they escape from their enclosing membrane, enter the thoracic muscles, and complete their cycle of development.

Morphology of the Parasites.—The adult worms are whitish in colour, long and filiform, with a smooth cuticle, a spherical head terminating in a simple round mouth. The tail is rounded. The male is smaller than the female, and measures $38{\cdot}6 \times 0{\cdot}12$ mm. The tail is curved.

The female is longer, thicker, and rather more transparent than the male, and measures 76 to $100 \times 0{\cdot}185$ mm. Two uterine tubes open from a single vagina and run nearly the whole length of the body. They contain eggs in all stages of development. The younger eggs are oval, measuring 50×34 μ. They contain a coiled embryo. The embryo enlarges and causes the egg-shell to elongate. Finally, they escape through the genital pore and enter the lymph stream and through the lymphatic vessels reach the blood. The microfilariæ measure from 280 to 320 $\mu \times 7{\cdot}5$ to $8{\cdot}5$ μ (Low). They are long, slender, cylindrical bodies, with a rounded anterior and a tapering posterior end. They are enclosed in a sheath which is not closely applied at the ends so that the filaria can move backwards and forwards within it. The anterior extremity possesses a proboscis carrying a minute apical spine capable of being covered by a six-lipped hood. Behind the extremity the body is covered by a transversely striated wall. Inside are closely packed cells whose nuclei are readily stained. In unstained specimens the central mass appears granular for the most part, but this granular aspect is interrupted by several "clear spots." There is a "break" in the cell column 50 μ from the head, a V-shaped irregular spot (Manson) 90 μ from the head, and a "tail spot" near the caudal extremity.

Pathology.—If the parent worms lie in positions in which they do not obstruct the flow of lymph, and if they are not accidentally injured, no symptoms may arise. Symptoms may, however, arise in two ways. Either the parent worms may mechanically obstruct an important lymphatic trunk, or the female worm, as the result of some injury, may abort and produce, instead of the elongated embryos, the comparatively broader oval eggs which may block up small lymph channels.

Sometimes coiled-up masses of worms may block up a lymphatic trunk. Considerable irritation and inflammatory proliferation may be set up, so that lymphatics may remain blocked after the worms have died and disappeared. The engorgement of the tissues lowers their

trophic power, so that inflammation and even abscess formation are not uncommon.

An interesting theory is that smooth-skinned elephantiasis (E. glabra) is due to blocking of the channels in the lymphatic glands, while rough elephantiasis (E. verrucosa), in which the skin is coarse and nodular, is due to blocking of small skin capillaries.

Symptoms.—Symptoms vary very greatly according to the part involved. Lymphangitis with cellulitis and erythema associated with fever is common. Lymphadenitis, usually inguinal, in which the glands are enlarged, soft, elastic and tender, often occurs. In some cases the glands may reach an enormous size. Microfilariæ may be obtained by aspiration with a hypodermic syringe. Lymphangiectasis is common and usually affects the scrotum (lymph-scrotum). The condition begins with fever and local inflammation. The part becomes swollen and elastic, and the skin shows clear vesicles containing lymph or chyle and showing embryos. Orchitis and hydrocele frequently occur.

Chylous Extravasations.—As the result of dilatation and rupture of lymphatic vessels extravasations of chyle may occur. A frequent seat of extravasation is the urinary passages, and chyluria or hæmochyluria results. Chylous diarrhœa, chylocele, and chylous ascites are more rare.

Elephantiasis.—As a sequel to repeated attacks of lymphangitis the affected part fails to return to its normal size, and in time may become greatly enlarged. The condition then becomes known as elephantiasis. The skin surface may be smooth or rough. The lower limb and the scrotum are the usual sites of the condition. Much more rare s elephantiasis of the vulva, breast, arm, or scalp. Pendulous circumscribed masses due to filarial disease have been noted in many situations.

Blood Changes.—The red cells show no changes unless there is hæmochyluria or severe diarrhœa which may lead to anæmia. A fair rise in the number of white cells may occur. Polymorphs, lymphocytes, and eosinophils are all increased in recent cases. The lymphocytes are most increased, so that the polymorph percentage seldom exceeds 70 per cent. Eosinophils vary from 4 to 10 per cent. as a rule, but as many as 70 per cent. have been recorded. Their numbers appear to correspond with the number of embryos in the circulating blood, and as these are usually most numerous at

night, eosinophils are then in greatest abundance. Gulland[1] made the following observations on the number of eosinophils per cubic millimetre in one case:—

11.10 A.M.	276	10.20 P.M.	808
3 P.M.	283	11.10 P.M.	1500
4 P.M.	476	11.20 P.M.	1224
10.10 P.M.	742		

The microfilariæ occur in the peripheral blood, but are only found at night. They begin to appear between 5 and 7 P.M. and increase till midnight. Only an occasional parasite is found after 7 or 8 A.M. They show wriggling and twisting movements and knock about the red cells, but they have no power of locomotion. Their numbers vary greatly. Manson states that as many as 500 may occur in a single film, but in most of the cases we have seen in this country, and in films sent us from abroad, the number is small.

In the daytime the microfilariæ live in the lungs and large thoracic vessels. The explanation of their periodicity in the peripheral circulation is not known, but obviously their presence there at night adapts them to the habits of the mosquito. The filaria of the South Sea Islands, which is identical with F. nocturna, shows no periodicity.

Treatment.—Treatment is purely symptomatic.

Filariasis Due to Filaria Loa

Filaria loa is a parasite of superficial fibrous tissue. Its chief endemic centre is the West Coast of Africa. The male is a slender transparent worm tapering to each extremity and measuring 25 to $34 \times 0{\cdot}27$ to 0·45 mm. The female measures 44 to $63 \times 0{\cdot}38$ to 0·5 mm. The microfilaria (known as Filaria diurna) measures 210 to 280 $\times 7$ to $7{\cdot}5$ μ. These embryos pass into the circulation by day and are not found at night, and their appearance in the peripheral blood is not altered by changing the habits of their host in regard to sleep. Their number is always scanty.

The embryos do not cause disease.

The adult filaria may cause slight local disturbance in the course of its wanderings in the connective tissues, and may give rise to movements visible on the surface. The symptoms are of more importance when a filaria finds its way into the conjunctiva or anterior chamber of the

[1] *Brit. Med. Journ.*, 5th April 1902.

eye. In these situations it may cause irritation and interference with vision. The evanescent tumours known as Calabar swellings are probably due to the presence of F. loa in the tissues. They are associated with marked eosinophilia.

Treatment.—When a filaria is localised by its movements or is seen in the eye it may be removed through an incision. Calabar swellings are best treated by local sedative applications.

Filariasis Due to Filaria Perstans

The adult worms usually lie free in the connective tissue of the abdomen. Microfilariæ pass from the uterus of the adult into the circulating blood. As the microfilariæ escape from their membrane they have active powers of locomotion. They measure 200 to 230 μ × 4·5 to 5 μ. A shorter type has been noticed.

There is no periodicity in their appearance in the peripheral blood. They are never numerous, and are not pathogenic.

Filariasis Due to Filaria Demarquayi

This parasite is found in certain West Indian Islands and elsewhere. The microfilariæ resemble the preceding variety except in the more pointed shape of the caudal extremity, which extends beyond the column of nuclei. They show no periodicity. The parent worms inhabit loose fibrous tissue and appear to be non-pathogenic.

Literature

See *Brit. Med. Journ.*, 15th November 1913.

CHAPTER XLIII

PIROPLASMATA—HÆMOGREGARINIDA—HALTERIDIUM—ANAPLASMATA

Piroplasmata

These parasites belong to the hæmosporidia. They are ovoid or pear-shaped, with one or two chromatin bodies. They are found in the red blood corpuscles. They multiply by dividing into two or more spores. Actively motile spores may be seen in the plasma. Piroplasmata do not produce pigment. They have not been definitely demonstrated in man, but affect horses, cattle, sheep, dogs, rats, fowls, etc. There are several different species, many of which cause pyrexia or hæmoglobinuria or both in animals. They are transmitted by ticks, which remain infective through several generations.

Literature

Fantham, *Quart. Journ. Micros. Science*, 1906, 1907. Nuttall and Graham Smith, *Journ. of Hygiene*, 1906, 1907 (P. canis). Castellani and Chalmers, *Manual of Tropical Medicine*, 1910.

Hæmogregarinida

Young forms are found in the red corpuscles of reptiles, amphibians, birds, and in a few mammals; older forms are found in the plasma. Sporulation occurs in the cells of liver, bone-marrow, and other organs. The chromatin is scattered throughout the nucleus.

Only part of the protoplasm divides into spores, which may accumulate in the distended parent cell. The parasites do not produce pigment.

Leucocytozoa are found in the dog, cat, rat, and palm squirrel.

Leucocytozoon canis is transmitted by ticks.

Literature

Castellani and Chalmers, *Manual of Tropical Medicine*, 1910, p. 319. Doflein, *Lehrbuch der Protozoenkunde*, 1909, 679. Porter, *Science Progress*, iii. 1910

(Leucocytozoa). Wenyon, *Parasitology*, iii. 1910 (Leucocytozoa). Henry, *Journ. of Path. and Bact.*, xiv. 1910 (Hæmoprotozoa of British Sea Fish). Welsh and others, *Journ. of Path. and Bact.*, xiv. 1910 (Hæmogregarinida of Australian Fauna). See also various abstracts, *Folia Hæmatologica*, iv. supplement, 1907.

Halteridium Danilewskyi

These parasites are found in the red corpuscles of birds. Schaudinn, in 1904, concluded that they were stages in the life-history of trypanosomes. A certain amount of support has been given by others to this view, but on the other hand most observers consider that Schaudinn was misled by a double infection of a halteridium and a trypanosome.

Literature

A good account of morphology is given by Welsh, *Journ. of Path. and Bact.* 1911.

Anaplasmata

A minute protozoal parasite, the *anaplasma marginale*, has been shown by Theiler to be the cause of the disease known as gall sickness which affects cattle in South Africa. Similar bodies affect cattle in North and South America. Anaplasmata were at one time thought to be a phase in the life-cycle of piroplasma bigeminum, but they appear to be distinct, although there is a close association between the two. Thus an animal inoculated with piroplasmata invariably develops anaplasmosis from twenty to thirty days after the red water reaction. A special variety, *anaplasma centrale*, has been discovered by Theiler, and its virulence seems to be less than that of the marginal parasite.

Anaplasmosis is transmitted by ticks. In South Africa, the blue tick, Boophilus decoloratus, is the carrier.

Anaplasmata are spherical bodies which seem to consist entirely of chromatin. They vary in size from a minute point to about 1 μ. Some of the bodies are marginal; some are central, but the majority are found a short distance from the edge of the red corpuscle.

Considerable discussion has arisen in connection with the discovery of similar bodies in the blood of a large number of domestic and wild animals. The question which arises is whether spherical intracorpuscular bodies staining like chromatin are to be regarded as anaplasmata or Jolly bodies. A large number of observations on different animals has been made by Dodd. He found very numerous chromatin bodies, varying in size from 1 to 4 μ, in marsupials, and considers that these

are normal appearances, although under certain conditions they may be present in abnormal numbers.

It may be concluded that between the pathogenic anaplasmata of cattle on the one hand, and the normal Jolly bodies of marsupials on the other, there is a group of chromatin bodies found in the red corpuscles of a large number of other animals whose nature must in the meantime be left an open question.

Literature

Dodd, *Journ. of Compar. Path. and Therapeutics*, xxvi. 1913, p. 97.

APPENDIX A

SPLENECTOMY IN PERNICIOUS ANÆMIA

While proofs of Chapter XIV. were in the press the question of treating pernicious anæmia by splenectomy began to assume some importance, and a number of cases in which improvement has followed the operation are now on record. Eppinger reports two cases in which there was an immediate rise in the number of red corpuscles which reached normal, an increase of body weight, and a disappearance of subjective symptoms.

V. Decastello records the case of a woman, aged 52, with typical symptoms and blood picture (red corpuscles, 1,236,000). Under treatment by the ordinary therapeutic measures the red cells fell to 750,000, Hb. 17 per cent. There was œdema, ascites, and drowsiness, and death seemed imminent. Splenectomy was performed. In ten days the œdema and icterus had disappeared. The blood showed a large invasion of normoblasts, and in eleven weeks the count had risen to 4,032,000 with Hb. 83 per cent.

Klemperer and Hirschfeld report three cases. One, a woman aged 63, died of bronchopneumonia. Both the others improved. In one the corpuscles rose from 950,000 to 1,730,000; in the other from 1,100,000 to 2,680,000. In all three there was an enormous normoblast reaction and a great number of corpuscles showing Jolly bodies.

Klemperer subsequently records ten cases. Two died immediately after operation. In eight there was improvement in health which was reflected in the blood, but in only one case did the blood picture of pernicious anæmia disappear.

Huber had a case in a woman, aged 34. She was at first too weak for operation, and was treated with intramuscular injections of defibrinated blood. There was temporary improvement, followed by a high temperature and the appearance of petechiæ. As a last resource the spleen was excised. She stood operation well, and rapidly improved. After five weeks erythrocytes numbered 2,500,000, Hb. 50 per cent. Three months afterwards the patient could walk, but prognosis was apparently not good. At a discussion in the Berlin Gesellschaft für Chirurgie, W. Türk stated that if in pernicious anæmia the spleen had an injurious action it was different from that in hæmolysis and some other agent had to be assumed. Splenectomy, however, played a part. Patients recovered at first, but the state of the blood never became normal again. Mühsam referred to eleven cases. One died from purulent bronchitis, two from a hæmorrhagic diathesis, one from myelitis; in a fifth the blood went from bad to worse. Six cases were alive, and had regained some strength, but were not in good health. It is unnecessary to refer to further cases.

The argument for the operation is based upon the good results obtained by splenectomy in Banti's disease, the suggestion that in pernicious anæmia there is a pathological exaltation of the normal function of the spleen in dealing with old and effete blood corpuscles, and a theory that the spleen produces a hormone which inhibits the action of the bone-marrow.

The first argument seems to us irrelevant, as there is no likeness between Banti's disease and pernicious anæmia. As regards the second, there is no doubt that the spleen takes up old and damaged red corpuscles, and that this function may be increased by the larger number of abnormal corpuscles brought to it in pernicious anæmia as suggested on page 123. In our researches on blood destruction in normal and spleenless dogs we found that damaged corpuscles were removed from the circulation more rapidly in animals with the spleen intact. Whether a case of pernicious anæmia is to be much benefited by the continued presence in the circulation of corpuscles which the spleen should have dealt with is open to question. The effect on the corpuscles is probably rather a delay of their funeral than an extension of their usefulness.

As regards the suggested inhibitory effect of the spleen on the bone-marrow we may say that there is no evidence in its favour, and in our splenectomy experiments the evidence was against it.

A point to be kept in view is that in some instances we have met with appearances of supplementary blood formation in the spleen in cases of pernicious anæmia.

A feature which makes judgment specially difficult is the capricious course of the disease, which we have already pointed out.

We have never had splenectomy performed, and only once recommended it. The case was that of a woman of 55 who eight months before had recovered in our wards under arsenic from a severe first attack of pernicious anæmia. She was brought in a second time in a very feeble condition, with the usual lemon-yellow pallor, fever, gastro-intestinal symptoms, and a rapid, feeble heart. The red count was 670,000, hæmoglobin 16 per cent. After five days, on small doses of arsenic, the reds rose to 780,000, hæmoglobin 20 per cent. A week later the count had fallen again to 650,000, hæmoglobin 16 per cent., and the general symptoms had only slightly improved. We proposed splenectomy as a last resort, as there seemed no chance of her recovery under ordinary measures, but the patient and her friends were most unwilling to allow operation. Some time was taken up by negotiations, and the blood was not examined, as it was intended to do it just before she went to the surgical side. She began to improve quite suddenly, and the next examination of the blood a fortnight after the last one showed reds 2,070,000, hæmoglobin 45 per cent., with great general improvement. Both blood and patient have steadily got better under arsenic by the mouth—of course along with the other usual measures—and the reds are now just under 4,000,000, hæmoglobin 82 per cent. Had the spleen been removed when we first proposed it the sudden improvement would certainly have been ascribed to the operation.

This case well illustrates the danger of drawing conclusions from too

narrow a basis, especially in a disease so uncertain in its prognosis as pernicious anæmia. The more recent statistics bring out both the dangers and the ultimate failure of the procedure to produce complete cure. Patient treatment along the ordinary lines would probably have produced results at least as good as those in Mühsam's series, and possibly better, certainly without so large a percentage of immediately fatal cases.

We conclude that as the seat of the disease is the bone-marrow and not the spleen, a cure is not to be looked for from splenectomy. The utmost benefit that can be expected from the operation is a stimulus to the marrow from hæmorrhage, and a moderate lengthening of the sojourn in the circulating blood of certain red corpuscles of doubtful value to their host.

We are unable to say that such benefit is ever likely to be worth the risk involved in obtaining it.

Literature

Eppinger, *Münch. med. Woch.*, 1913, p. 1236; *Berlin. klin. Woch.*, 1913. V. Decastello, *Wein. klin. Woch.*, 1913, p. 951. Klemperer and Hirschfeld, *Therapie d. Gegenwart*, 1913. Klemperer, *ibid.*, 1914, p. 1. Huber, *Berlin. klin. Woch.*, 1913. Türk, *Deut. med. Woch.*, 1914, p. 371. Mühsam, *Deut. med. Woch.*, 1914, p. 377. Ranzi, *Münch. med. Woch.*, 1913, p. 2819. Barbier, *Bull. de la Soc. de Méd. de Paris*, 1913, p. 355. Harpole and Fox, *Surg. Gynec. and Obstet.*, 1914.

APPENDIX B

A NEW STAINING METHOD

In examining films of myelocythæmia, one finds that none of the single stains in ordinary use are sufficient to give a complete picture. Ehrlich's triple stain gives the best picture of myelocytes, but has the disadvantage that lymphocytes are very poorly stained, and the basophil series not at all. On the other hand, it is very difficult, in films stained with Jenner, to distinguish with certainty between some of the myelocytes and the cells of the lymphocyte series. With Leishman and other Romanowsky stains, the difficulty is even greater, and one finds the differential counts made with Ehrlich on the one hand, and a Romanowsky stain on the other, from the same blood, show wide differences even in the hands of skilled observers. We find that this difficulty can be got over by combination of the triple stain and Jenner. The films are fixed with heat, and we prefer to use Cabot's method of doing so, bringing the films to 140° C. in an oven with fair rapidity, and then allowing them to cool rapidly. Stain with triple stain for three to five minutes or longer, wash quickly in distilled water, then in Jenner, without

previous drying, for a minute or such time as may be desirable from the known strength of the solution. Wash again in distilled water and allow to dry. Mount in balsam. The Jenner reinforces the nuclear stain throughout, though, as is always the case with heated films, nuclear structure is not so well preserved as with the methyl-alcohol fixing alone. The myelocytes, polymorphs, and eosinophils retain the triple character of staining, as do also the red cells, but in addition, the basophil granules are well brought out, and in particular those of the basophil myelocytes, which with Jenner alone are apt not to be preserved, but which are evidently fixed by the heat. Some of the basophils, as Kanthack and Hardy pointed out long ago, are explosive, and their granules are found scattered round the nucleus. The cells of the lymphocyte series show the characteristic blue staining of the cell body, and generally one attains an amount of detail in this way which we have not seen by any other method. Leishman does not make so satisfactory a combination. The characteristic red stain of the chromatin is not brought out, and it acts like a rather diffuse Jenner stain. If by any chance films have been overheated, the staining can still be carried out by warming the film while it is being stained with Ehrlich, and by adding a few drops of water to the Jenner stain in its turn, and heating that also. One can, indeed, get very satisfactory preparations in this way, as the overheating fixes the granules exceedingly well.

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